PRESBYTERIAN-ST. LUKE'S HOSPITAL

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Arsine Induced Anuria

Intracorporeal Hyperthermia

Mithramycin Therapy of Cancer

Intestinal Submucosal Carcinogens

Nitrate Therapy in Experimental Coronary Occlusion

Focal Freezing of the Central Nervous System—Review Article

Abstracts and Reviews

THE PRESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLET

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Address communications:
Editor
Presbyterian-St. Luke's Hospital Medical
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ARSINE INDUCED ANURIA

Robert C. Muehrcke, M.D.
Gordon D. Lucas, M.D.
Conrad L. Pirani, M.D.

Arsine (AsH_3) is one of the most toxic gases known. For this reason, it has been incorporated in the war gas Lewisite (B-chlorovinyl dichloroarsine). It is colorless, inflammable, heavier than air, unstable and is a strong reducing agent. Textbooks of chemistry describe it as having an odor like garlic, however, most victims are unaware of any unusual odor [1,2,3]. The toxicity of arsine is roughly proportional to the amount of exposure. The heavier the exposure, the sooner the onset and the graver the prognosis. If inhaled for 30 minutes in a concentration of 250 parts per million, it is lethal to man[4]. With excessive exposure, severe hemolysis occurs and an early death usually results from pulmonary edema. Should the individual survive the initial hemolysis, fatal anuria may develop.

OCCURRENCE

The toxic properties of arsine were first described in 1815 by Gehlen[5,6], a Munich metallurgical chemist. He "inspired a small portion" of arsine and within one hour he was seized with vomiting, chills and fever. Nine days later he died. "Unfortunately, this tragic accident is repeated from time to time"[2]. Subsequently, arsine poisoning has occurred in experimental metallurgical chemists, laborers in the aniline dye industry, makers of toy balloons, workers in the smelting and refining industry, storage battery workers, sailors of the submarine service, and in laborers cleaning tanks used for storing or transporting strong acids[4,7-10]. The highest incidence of arsine poisoning has been in the metallurgic industry[11]. Arsenic is a common contaminant of commercial metallic ores, such as gold, tin, zinc, lead, iron, aluminum and copper[12-14], and arsine is evolved when hydrogen generated by the wetting of metallic dross reacts with the arsenic contaminant[15,16].

MECHANISM OF TOXICITY

Arsine usually enters the blood stream through the lungs. Because of its strong reducing properties, it rapidly combines with hemoglobin within the erythrocyte[17]. After a short latent period hemolysis occurs. Oxygen was found essential in this reaction of arsine and hemoglobin in producing hemolysis[18]. In 1937, Labes[19] suggested that in the presence of oxygen, arsine is oxidized within the erythrocyte to a colloidal elementary arsenic which combined with hemoglobin to produce hemolysis. However, Haubner and Wolff[18] considered arsenic

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From the Renal and Nutritional Unit, Department of Medicine, Presbyterian-St. Luke's Hospital, and from the Departments of Medicine and Pathology, University of Illinois College of Medicine, Chicago.

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dihydride to be the hemolytic agent. In addition, their data further indicated that the final product of oxidation of arsine was arsenious acid. Gebert[20] believed that arsenic dihydride was not the hemolytic agent but only an intermediate product in the oxidation of arsine to elementary arsenic. He found that elementary arsenic-hemoglobin was the final product that produced hemolysis. The liberated "arsenic-hemoglobin" molecules pass through the glomerular filter and subsequently oliguria or anuria develops which may be the result of one of the following mechanisms, either singly or in combination: (1) It is thought that arsenic-hemoglobin or a arsenic-hemoglobin haptoglobin complex precipitates in the lumen of the nephron[16] to produce the nephrotoxic lesion described by Oliver[21] i.e., a uniform necrosis of the renal tubular epithelium down to, but not including, the basement membrane. (2) Hypoxia secondary to the hemolytic anemia may produce an ischemic tubular lesion such as described by Lucké[22]. This lesion produces necrosis of tubular cells, fragmentation of the tubular basement membrane and leakage of the tubular content into the interstitial space. (3) Inhibition of renal tubular cell respiration may occur as a result of the direct effect of arsine on intracellular respiratory enzymes[23].

CLINICAL FEATURES

The symptoms of arsine poisoning result from the hemolysis of erythrocytes. Arsine poisoning should be suspected in any industrial worker who suddenly develops jaundice, anemia or clinical evidence of renal disturbances[4,24]. Following exposure to arsine there is usually a delay of 2-24 hours before the onset of symptoms. The sequence of symptomatology is as follows: First there is a vague sick feeling and nausea. Then, the patient develops cramping abdominal pains, vomiting, weakness, tingling of face, hands and feet, and headache. Costovertebral pain is followed by passage of a dark urine[6]. Finally, the patient complains of marked weakness, fatigue, becomes feverish, dyspnic and lethargic. With the development of hemolytic anemia, jaundice appears which may be an intense coppery bronze in color. At times the color of the skin may have a bluish hue. This skin color may result from either met-hemoglobinemia or cyanosis. Finally, pulmonary edema and cyanosis appear and are followed by lethargy, coma and death.

TREATMENT OF ARSINE INDUCED ANURIA

Whole blood transfusions were administered to patients with severe arsine toxicity to replace the erythrocytes lost by hemolysis. This usually prevented patients from developing pulmonary edema due to the hypoxic effects of the hemolytic anemia only for them to develop anuria and subsequently die in uremia[12]. In 1957, McKinstry and Hickes[25] suggested the use of massive exchange transfusions as a rational method of treatment which could remove large quantities of the arsenic-hemoglobin complex and erythrocytic debris and also restore the red cell mass. In 1961, Neuwirtová and co-workers[26] used this treatment in one of three patients with arsine induced anuria. However, he died in uremia 14 days after exposure despite a single hemodialysis.

Gaultier and Reymond* in 1949 first used peritoneal dialysis in the treatment of patients with arsine induced anuria, but they appeared to have no success with this treatment. In 1958, Ullrich[27] used the Alwall extra corporeal hemodialysis unit to treat one patient. He found it necessary to dialyse four times over a 21 day period before his patient made an apparent complete recovery. He also reported in detail the therapeutic and supportive measures taken in the management of his patient. In 1961, Neuwirtová[26] used extra corporeal hemodialysis in the treatment of three patients with arsine induced anuria. One survived but developed chronic renal disease.

In general the therapy of patients with

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*Quoted by Neuwirtová[26].

arsine anuria has not been very successful and in the past constituted a difficult and almost impossible therapeutic problem. The case reported below describes modern and successful management of a patient with arsine induced anuria.

Case Report: A 32 year old husky truck driver delivered a mixture of sodium hydroxide and arsenite trioxide in an aluminum tank trailer truck. After he emptied the tank, he crawled into it and for approximately 30 minutes flushed out the residual liquid with water. Arsine was evolved by the reaction of the aluminum wall of the tank with sodium hydroxide and arsenite trioxide. Two hours later the patient felt sick. Four hours after arsine exposure, he vomited and was jaundiced. At twelve hours, he had costovertebral angle pain and a few hours later, he passed dark urine. Twenty-four hours after exposure, he was completely anuric.

On the second day after exposure, he was admitted to Presbyterian-St. Luke's Hospital. He was semi-comatose; his skin was an unusual bronze color tinged with blue. His pulse rate, temperature and blood pressure were normal. His liver was enlarged and tender. Marked tenderness was noted over both costovertebral angles. His hemoglobin was 7.5 grams, one-third of which had been liberated into the serum as free hemoglobin. There was 0.5 grams of methemoglobin per 100 ml of blood. The

Clinical Findings of a Patient Ill with Acute Oliguric Renal Failure Due to Arsine Poisoning

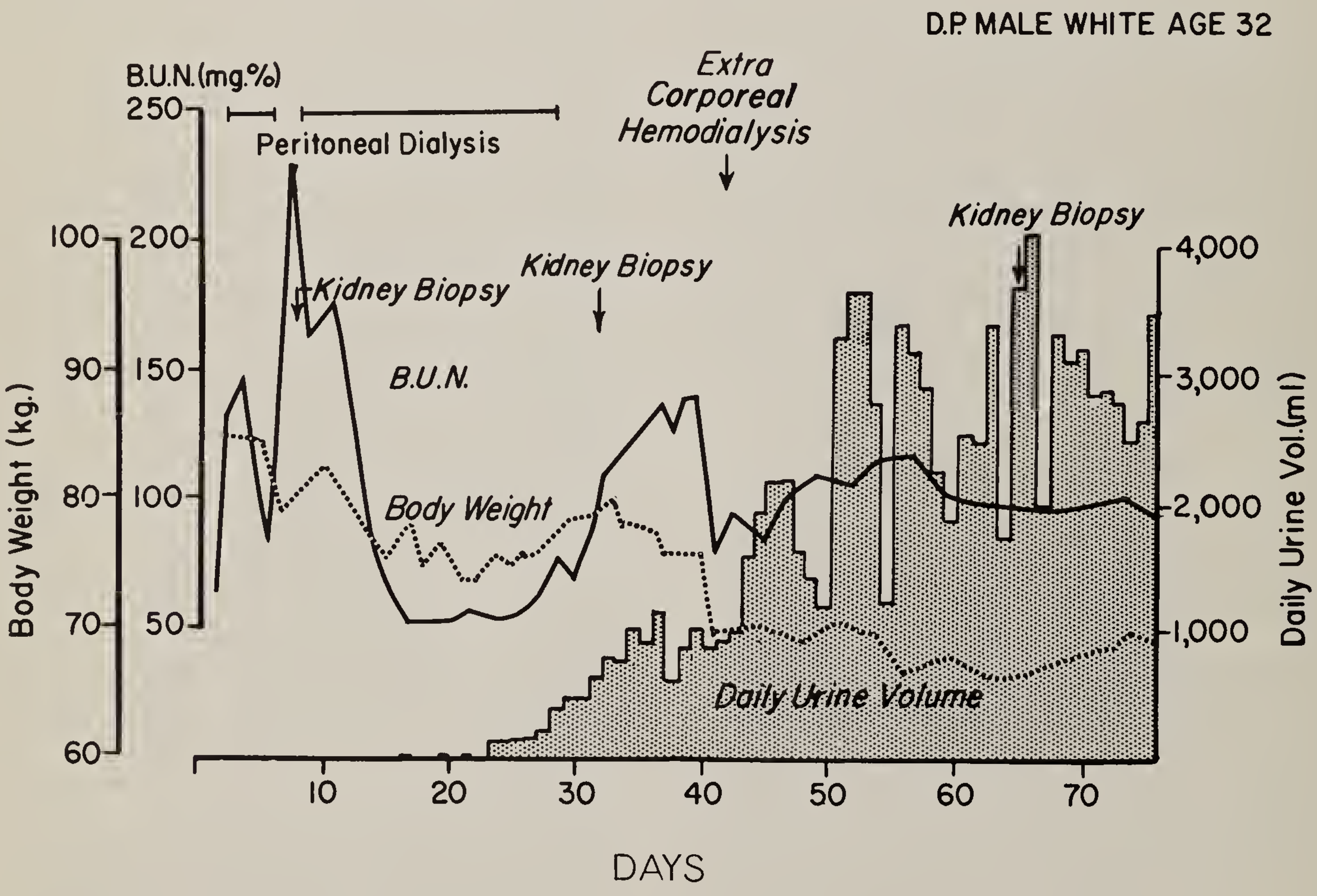

Fig. 1.—The clinical findings of a patient ill with acute oliguric renal failure due to arsine poisoning are charted over a 74 day hospital period. On admission, 19 units of whole blood were exchanged to remove the "arsenic-hemoglobin complex". The patient's life was sustained by use of peritoneal dialysis over a 26-day period. During this period, it was necessary to administer salt-poor human serum albumin to maintain the serum albumin levels. In addition, intramuscular injections of Vitamin K were given to restore the prothrombin time to normal. Although the patient survived the initial renal injury, he developed chronic renal disease.

serum sodium, chloride, potassium and CO_2 combining power were all normal. The blood urea nitrogen was 135 mg/100 ml.

The patient's hospital course over the next 74 days is illustrated in Fig. 1.

Peritoneal dialysis was started and an exchange whole blood transfusion was given. This was done as follows: one unit of blood was removed and one unit was administered. In all, 19 units were given. This removed large quantities of the "arsenic-hemoglobin complex" and greatly improved the clinical state of the patient. The next morning he appeared alert and active. The hematocrit and tests of hepatic function (B.S.P., prothrombin time, serum proteins, thymol turbidity) were normal. Abnormally high levels of arsenic were found in the blood obtained during the exchange transfusions. On the fifth hospital day, peritoneal dialysis was stopped and a right percutaneous renal biopsy was done. Study of the renal tissue revealed severe degenerative changes or destruction of the lining epithelium of the convoluted tubules (Fig. 2). Some tubules contained large hemoglobin casts. In other tubules, erythrocytic casts were noted. The interstitium was edematous and contained a few inflammatory cells. Mild hypercellularity of the glomeruli was present.

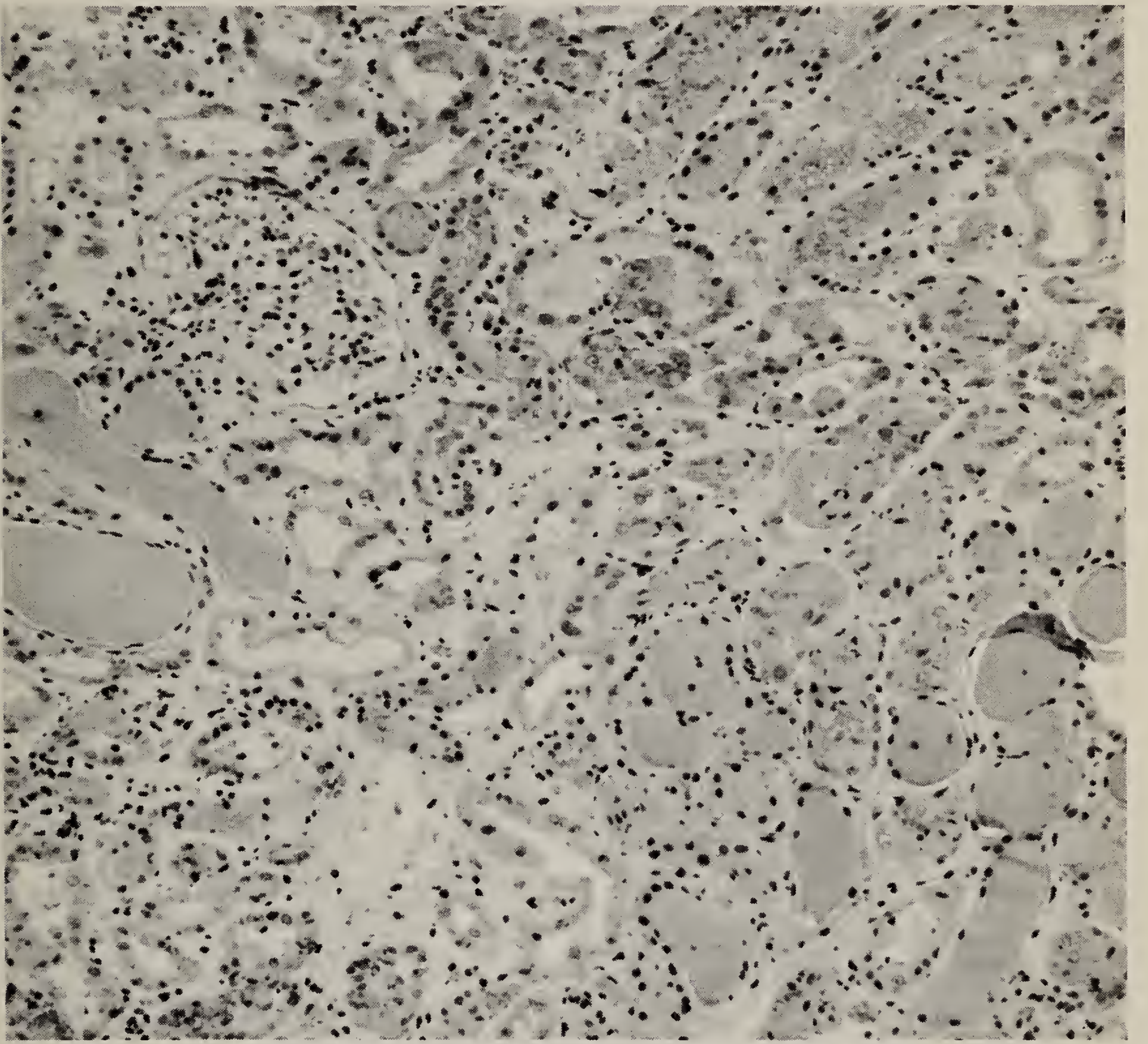

Fig. 2.—Acute Tubular Necrosis (H & E x 110) First renal biopsy taken 7 days after arsine exposure. There is either necrosis or severe degenerative changes of the lining epithelium of many convoluted tubules. Some tubules contain large casts and others pigmented casts. Few tubules exhibit regenerative activity of the lining cells. The interstitium is moderately edematous and contains a few acute and chronic inflammatory cells. There is mild hyper-cellularity of the glomerulus.

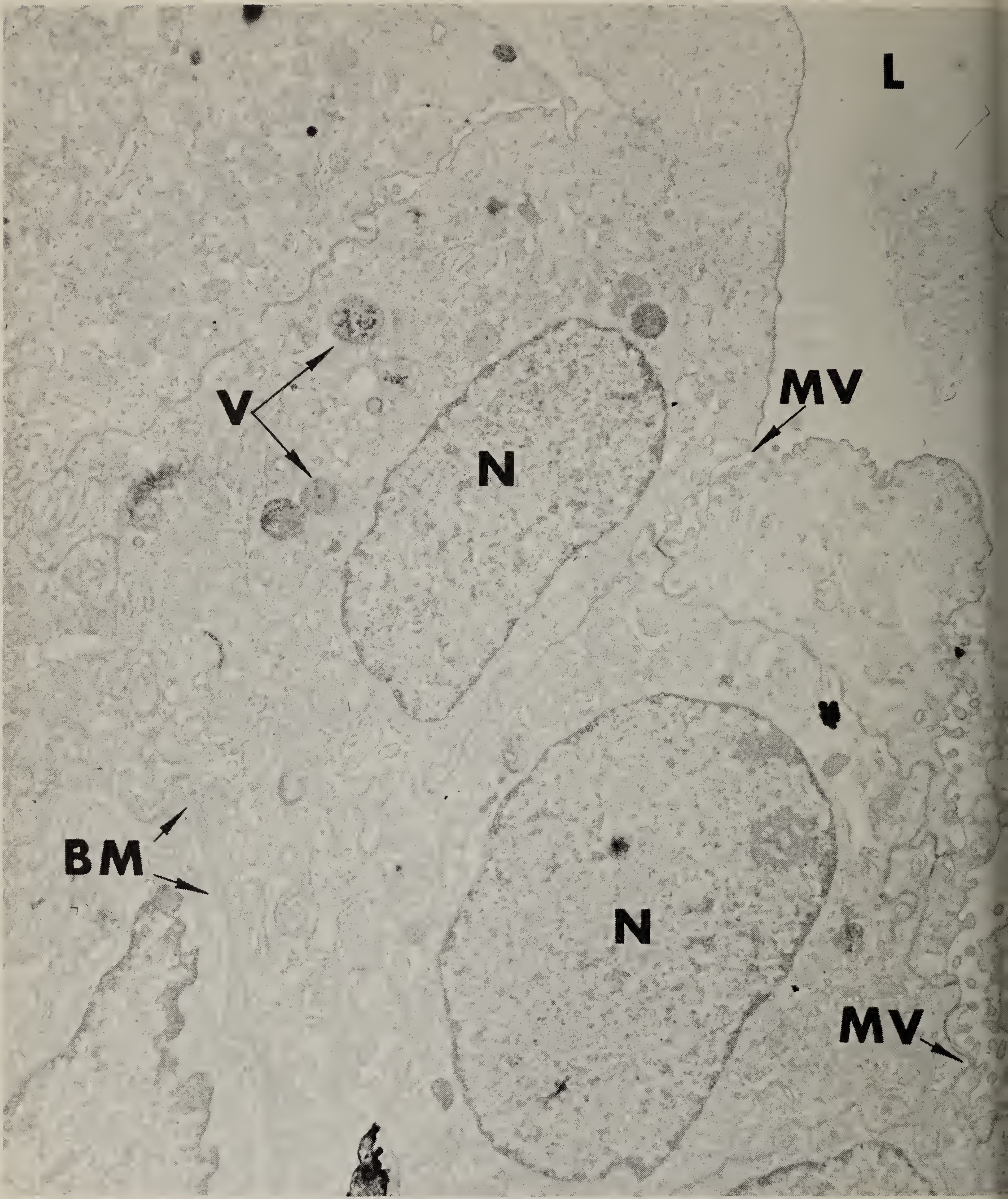

Fig. 3.—Electronmicrograph of Second Renal Biopsy (X7728) Thirty-one days after developing arsine induced anuria, regeneration of tubular cells was seen by light and electronmicroscopy. In this proximal convoluted tubule, the nuclei (N) of the lining cells are large. Although small, microvilli (MV) can be seen in the intercellular crypts, note the normal brush border is not present in the tubular lumen (L). Numerous vacuoles (V) containing ferritin are visible within the tubular cells. Note the normal appearing tubular basement membrane (BM).

On the 7th hospital day, peritoneal dialysis was restarted and was continued to the 28th hospital day. There was no abnormal levels of arsenic in the fluid removed during peritoneal dialysis. On the 30th day, diuresis occurred. Throughout the period of peritoneal dialysis, the patient received a high carbohydrate, high fat, low protein, low phosphorus, low potassium diet.

The serum albumin fell to 2.2 grams/100 ml and the prothrombin time was 5% of normal. In addition to supplements of Vitamin K, 200 grams of salt-poor human serum albumin was given. The serum albumin levels and prothrombin time were restored to normal.

On the 31st hospital day when early diuresis occurred, a second renal biopsy was done. Renal tissue was studied by light and electron microscopy (Fig. 3). The glomerular basement membrane was thickened. Regeneration of the lining cells was noted in many convoluted tubules. Interstitial fibrosis was noted. Hemoglobin casts were seen within some of the tubules. On electron microscopy, the mitochondria had an abnormal appearance and no brush border was seen in the proximal tubules. Numerous vacuoles containing ferritin and hemosiderin were seen within many tubular cells.

On the 38th hospital day, there was a rapid deterioration of the clinical state associated with uremic pneumonitis. After 6 hours of extra corporeal hemodialysis, the patient improved. On the 64th hospital day when the peak of diuresis occurred, a third renal biopsy was done. Morpholigical studies indicated tubule cell atrophy and repair associated with increased interstitial fibrosis and thickening of the basement membrane of the glomeruli and the convoluted tubules. However, the basement membrane of the collecting tubules was *not* thickened. On the 74th hospital day, the patient was discharged. His blood pressure was normal. The BUN was 79 mg/100 ml, the hematocrit was 24% and the fifteen minute excretion of intravenous injected PSP was zero. On the 161st day, when the blood urea nitrogen was 61 mg/100 ml, a fourth renal biopsy was done. There was severe interstitial fibrosis and tubular atrophy with further thickening of the convoluted tubular and glomerular basement membrane (Fig. 4). By electron microscopy, the proximal tubule had a short brush border and normal appearing mitochondria. Vacuoles containing ferritin were present (Fig. 5).

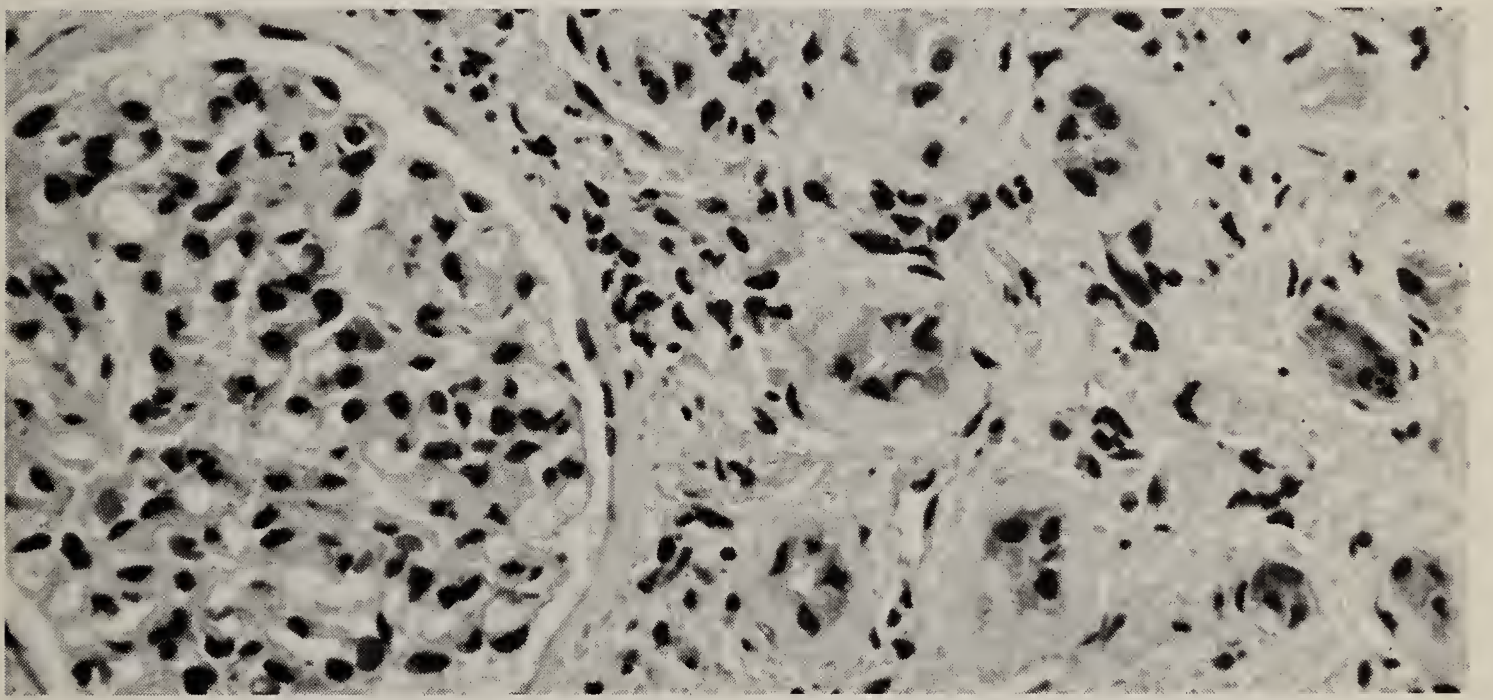

Fig. 4.—Convoluted tubular basement membrane thickening and interstitial fibrosis (H & E x 375). Fourth renal biopsy taken 161 days after arsine exposure. The convoluted tubules are markedly atrophic and surrounded by a thick basement membrane. There is severe fibrosis of the interstitium with a moderate infiltration of chronic inflammatory cells. In the glomerulus, there is a pronounced diffused thickening of the capillary basement membrane.

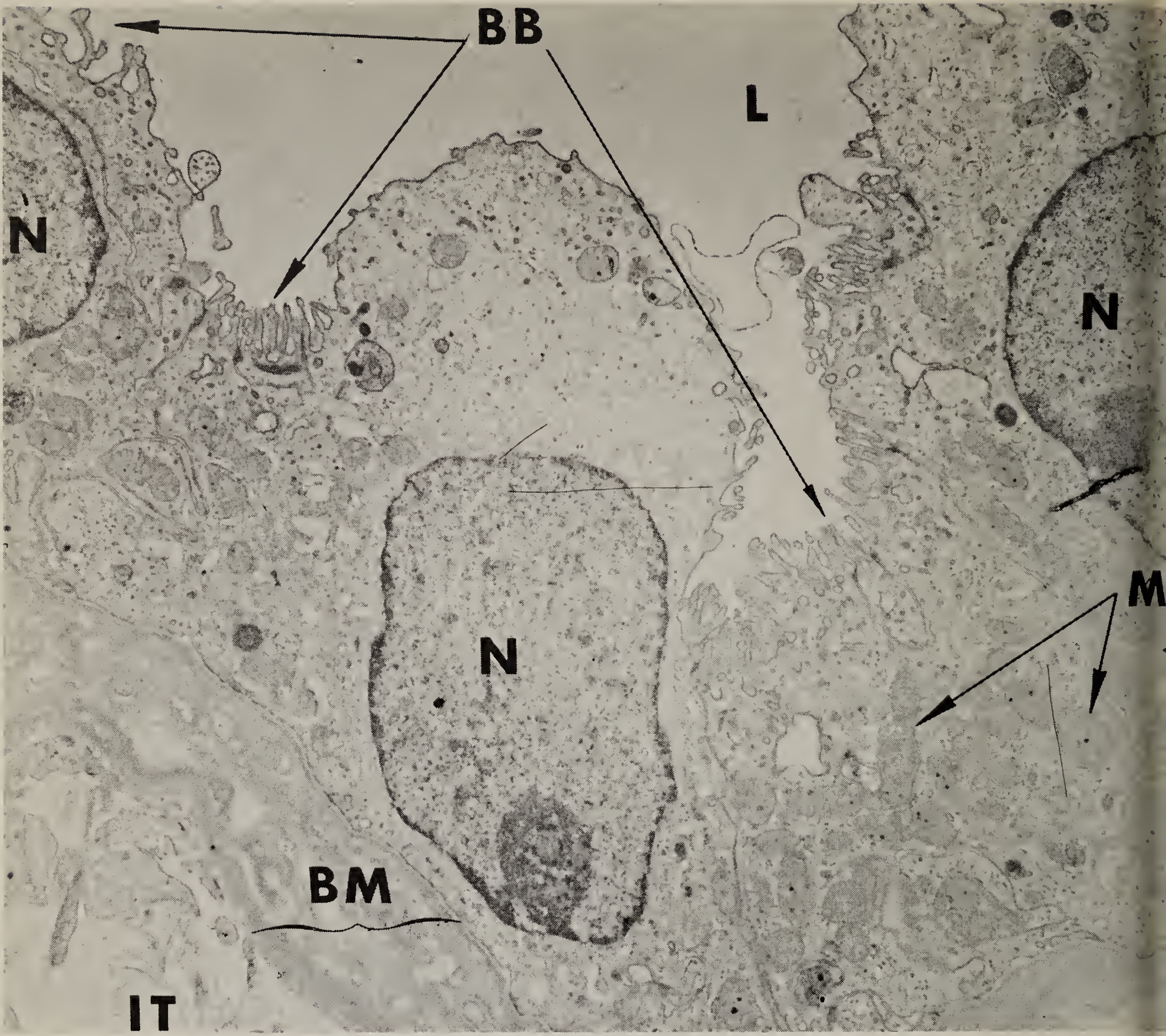

Fig. 5.—Electronmicrograph of Fourth Renal Biopsy (X7728). The fourth renal biopsy was taken 161 days after developing arsine induced anuria. The nuclei (N) are large and occupy a large portion of each cell. A new brush border (BB) extending into the tubular lumen (L) and consisting of short villi is seen especially in the intercellular crypts. The mitochondria (M) appear normal. A markedly thickened and split tubular basement membrane (BM) is clearly seen. The fibrotic interstitial tissue (IT) is increased.

DISCUSSION

The above patient was successfully treated for arsine induced anuria. The clinical course of the patient demonstrated the importance of prompt and intensive therapy of any individual exposed to a lethal dose of arsine. As emphasized by McKinstry and Hickes, the treatment should be of an emergency nature[25].

It should be pointed out that the compound 2, 3-Dimercaptopropanol (British anti-Lewisite—BAL—) is of no value in the treatment of arsine poisoning[24,28]. Moreover, BAL is a nephrotoxic substance, especially in a patient with anuria. McKinstry and Hickes[25] and Pinto and co-workers[9] found that BAL failed to stem the erythrocyte destruction and prevent subsequent anuria.

Because the "arsenic-hemoglobin complex" does not cross either the peritoneal membrane, or the cellophane membrane of the extra corporeal hemodialysis unit[17], it cannot be removed by either peritoneal or hemodialysis. Exchange transfusions given early in the treatment of the patient reduced the circulating "arsenic-hemoglobin complex" and red cell debris. This appears to have prevented excessive irreparable damage to the convoluted tubules. Exchange transfusions also restored the patient's red cell mass to normal, thereby preventing an additional hypoxic insult to the nephron.

The patient's life was sustained by peritoneal and extra-corporeal hemodialysis until renal function had been restored. Because dialysis was continued over a prolonged time, protective isolation was enforced to prevent the patient from developing a hospital borne infection. In addition, repeated observations were made of the prothrombin time, and serum albumin levels, and cultures were taken to detect possible bacterial infections (e.g. peritonitis, septicemia, pyelonephritis and lung infections).

As in other patients with acute renal failure, every effort was made to minimize protein breakdown and hyperkalemia by appropriate diet therapy which maintained the nutritional integrity of the patient. Although we usually supply fat and water soluble vitamins, in this patient, Vitamin K deficiency developed. This was found by studying the prothrombin levels serially and was corrected with parenteral Vitamin K.

PROGNOSIS

The mortality of arsine poisoning is reported as 20% by Kober and Hayhurst[29], as 31.4% by Glaister[3], as 28% by Hunter[2], and as 20-31% by Locket[30]. It is possible that these mortality rates are artificially high because fatal cases tend to be reported.

In general, the prognosis of the patient with arsine toxicity depends on the degree of damage inflicted on the kidney and is directly related to the patient's urinary output. Once anuria develops, the mortality approaches 100%[2,6,31,32] and death occurs between the 4th and 12th days[2,6,9].

The above patient, the patient reported by Ullrich[26], and a patient who survived arsine induced anuria reported by Neuwirtová and co-workers[26], appears to be the only follow-up case reports of individuals who survived arsine induced anuria. Ullrich's patient was described as being well eighty days after arsine exposure and without evidence of kidney damage. The patient of Neuwirtová and colleagues was anuric for 14 days before diuresis occurred. One year after exposure, "his azotaemia was normal", but the glomerular filtration rate was reduced to 52 ml/min. The kidneys concentrated urine to a maximum specific gravity of 1.017. These abnormal tests of renal function indicate a residual chronic disease. In time, both patients may die of renal damage as a direct result of arsine toxicity.

SUMMARY AND CONCLUSIONS

1. Arsine poisoning may produce a combined nephrotoxic and an ischemic renal lesion, which is manifested by oliguria or anuria.

2. If untreated, arsine induced anuria is usually a fatal disease.

3. Treatment consists of massive exchange whole blood transfusions to remove the "arsenic-hemoglobin complex" and restore the circulating red blood cell mass to normal.

4. In addition, dialysis should be done when necessary to sustain the life of the patient until renal function is restored.

5. Supportive nutritional and medical measures are used as needed.

6. To date, of the 3 patients who have survived the acute anuria, 2 have developed chronic renal disease.

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FACTORS PRODUCING INTRACORPOREAL HYPERTHERMIA IN AN ELECTROMAGNETIC FIELD

William D. Shorey, M.D.

Russell C. Hanselman, M.D.

R. Kennedy Gilchrist, M.D.

Robert W. Sessions

In 1941, one of us, (R.K.G.) noted that persons whose incisions had been closed with steel sutures incurred thermal injury around these sutures when in close proximity to strong magnetic fields. The concept was then developed that localized heating of tissue deep in the body could be selectively produced. The form of heating found to be most easily controlled in the human body as a result of an electromagnetic field was found to be hysteresis. This is the production of heat by the effect of a strong electromagnetic field on small particulate permanent magnetic particles. Three problems then required to be solved:

1) The target material must be innocuous to the body tissues, yet respond to an electromagnetic field with the production of heat. A permanent magnetic iron oxide Fe_2O_3 was found most successful. 2) The size of the particle must be small enough to pass through the lymphatics and capillary beds, i.e., between 0.1–0.01 micra in diameter. Larger particles than this clumped causing obstruction. As thermal response to an electromagnetic field is based on the volume of the mass of the particulate matter, high powered fields were required as the mass varies as the cube of the radius. 3) The frequency of the electromagnetic field was found to be critical. High frequencies are absorbed on the surface of organisms and do not penetrate into the center of the tissues; though in general they produce greater thermal response. A frequency of 55–100 Kc. was discovered to produce the required depth of penetration and heat production at the strength of 500 oersteds.

On the basis of these experiments a four inch coil was constructed in 1959 to test the practicality of such a theory in rabbits. Experiments were developed to determine the amount of Fe_2O_3 needed to produce thermal injury to living tissue. In rabbits, gelatin capsules of 1 cc. volume containing measured amounts of iron oxide were inserted between the rectus muscle and the posterior fascia and peritoneum. A similar series of gelatin capsules without iron under the contralateral rectus muscle served as a control. It was found that approximately 1 mgm. $Fe_2O_3\%$ caused thermal injury at 7 minutes irradiation without evidence of thermal injury on the control side.

Thermistors were developed which could be permanently placed in various organs of the experimental animal and by which temperature readings could be determined at will over periods of time up to nine months both in and out of the strong electromagnetic field without being affected by the field itself. Ceramic thermistors connected to very fine nonreactive copper wire leads incased in

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From the Department of Surgery

Supported in part by U.S.P.H.S. C-2282-08

polyethyline tubes 2 mm. in size were developed. These were placed in a Wheatstone bridge circuit and the temperatures recorded on a standardized continuous recording galvanometer. The accuracy of temperatures was found to vary between plus and minus .2–.5 C° depending upon the maximum and minimum temperatures to be measured. The work to be reported in the following paper was designed to overcome the side affects of the electromagnetic field to permit longer periods of irradiation of the experimental animal.

In our previous work on the subject of localized heating in the intact animal[1], we reported that the stomach had a more rapid thermal response than the kidney, liver, or spleen (Fig.1). When we analyzed the causes of death of the rabbits which were subjected to the same electromagnetic field used in the above mentioned experiment (1,500,000 volt ampers at 120KC. producing a field strength of 450 oersted, for periods of time over our $M.L.D._{50}$ of six minutes) perforation of the stomach was the most frequent cause of death with necrosis of the colon being next most common. The pathology in these rabbits was similar to that reported as causing the death of a human being inadvertently exposed to a strong Radar frequency field.

In an effort to prolong the time that experimental animals could tolerate such a field without injury it became necessary to determine the cause of the heating in the gastrointestinal tract, the type of electrical response producing the rise in temperature and whether this could be altered to prolong the time that the animals could tolerate such a field.

METHOD

Adult male white rabbits weighing 2–2.5 Kg. were prepared in the following manner. Thermistors previously described[1] were implanted in the body of the right lobe of the liver and in the anterior wall of the stomach; the serosa of the latter being folded over the distal one centimeter of the thermistor. A #14 mushroom type Latex rubber catheter was inserted through the anterior wall of the stomach. Through this a thermistor was placed just inside the stomach. A fourth thermistor was used either to

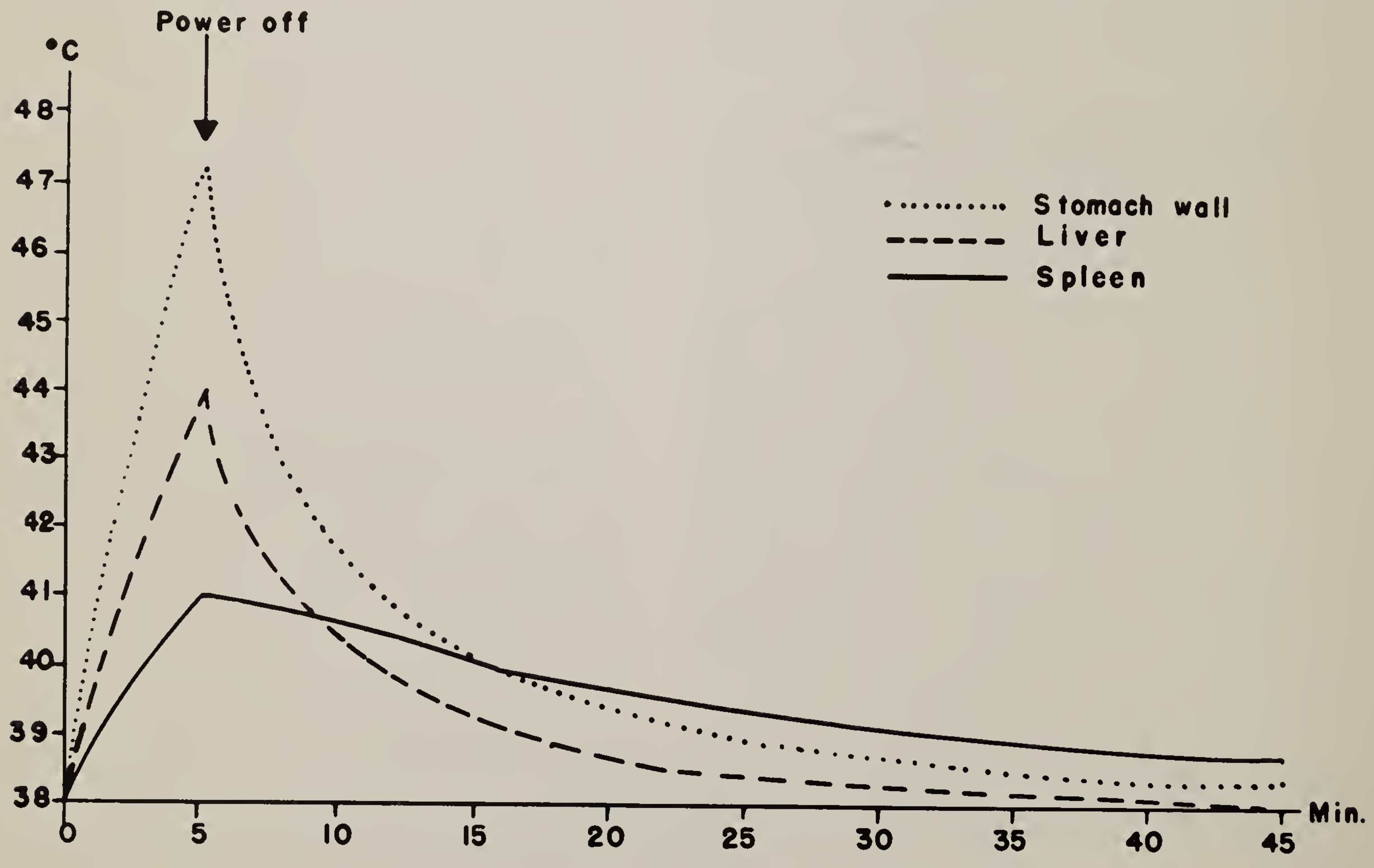

Fig. 1.—Graph of first experiments showing comparative rise in temperature of stomach, liner and kidney in rabbits.

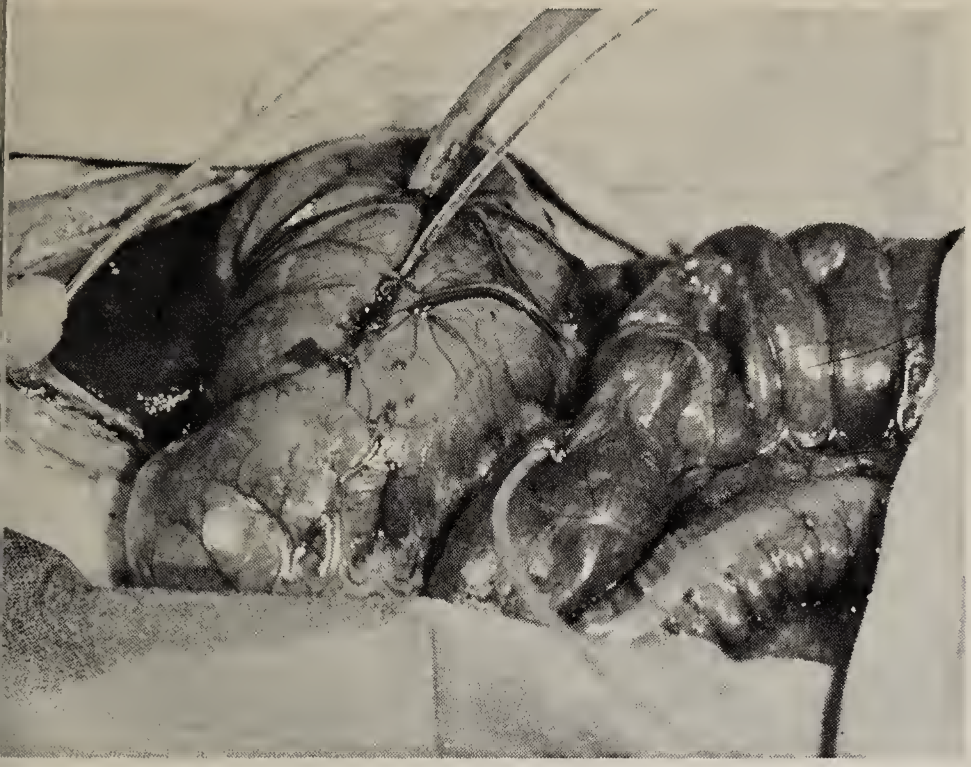

Fig. 2.—Abdominal contents of rabbit showing thermistors in liver, stomach and transverse colon. Gastrostomy tube in stomach behind thermistor.

monitor the rectal temperature or was imbedded in the wall of the transverse colon. (Fig. 2) Continuous recordings were made throughout the period of irradiation and for variable lengths of time necessary for the organs to return to normal temperatures.

The duration of each experiment was seven minutes unless the rise in temperature, as recorded by the thermistor in either the stomach or colon, approached 47°C. Temperatures of this magnitude were found to cause necrosis of the bowel in most cases if present for more than one minute. Each animal was subjected to the electromagnetic field for a minimum of five times, each acting as its own control. The basic diet of the rabbits was Staley's Rabbit Food. Five to seven days elapsed between successive exposures to permit recovery of normal intestinal function.

EXPERIMENTS AND RESULTS

The first series of rabbits subjected to this electromagnetic field served as controls. They were tested at least one week following placement of the thermistors. They demonstrated an average rise of temperature in the stomach of 5.36 C° with a range of 4–7.5 C°. (Fig. 3) The second series of animals was fed a regular diet for five to seven days and then aspirated and irrigated through the gastrostomy tube with distilled water until the stomach was empty just prior to irradiation. The average gastric rise in temperature was 2.3 C° with a range of 1.8–3.4 C°. The third series of animals was treated similarly except that physiologic saline was used for gastric irrigation. This series demonstrated an average rise gastric temperature of 2.2 C° with a range of 1.6–3.0 C°. The fourth series of rabbits tested was given a change of diet, i.e., carrots and cabbage because silica was present in the normal diet. This group of animals demonstrated an average rise of gastric temperature of 4.5 C° with a range of 4.1–4.8 C°. The fifth series of animals was a final control group run to exclude a loss of ability of the tissue to respond to this electro-

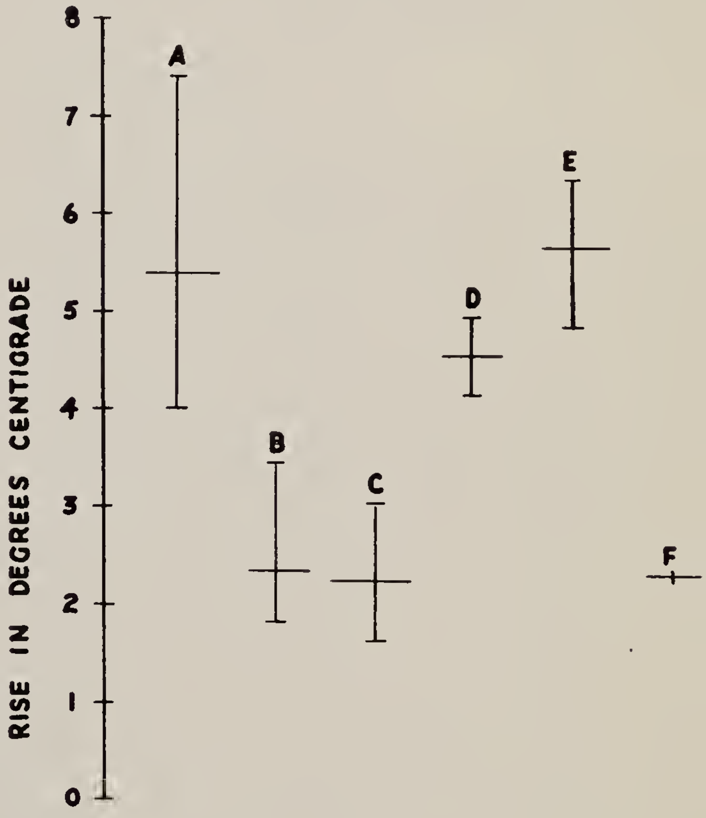

Fig. 3.—Graph of results of temperature increments in stomach: A) Fed control; B) Fed, aspirated and washed with Na Cl; C) Fed, aspirated and washed with H_2O; D) Fed on carrots and cabbage one week; E) Final fed control; F) Starved only one week.

magnetic field. This group showed an almost identical mean rise in gastric temperature as in the first control run, of 6.1 C° with a range of 4.8–6.3 C°. In a final series the rabbits were starved for one week prior to the experiment. This series demonstrated a mean rise of gastric temperature of 2.3 C°.

In Figure 4 comparable results are shown in the series of animals in which the thermistor was placed in the wall of the transverse colon, as previously shown in Figure 1. The average rise in the control period was 4.2 C° with a range 1.7–7.5 C°. The colon of the rabbit was then emptied by witholding food for one week and by the instillation of a solution of cascara sagrada through the gastrostomy tube on three occasions two days apart. In those animals which developed diarrhea, and on exploration had an empty bowel, the mean rise in temperature was 1.75 C° with a range of 1.1–2.5 C°. Figure 5 shows how similar is the rise of temperature of the liver, spleen, kidney, empty stomach and empty colon in response to seven minutes in this electromagnetic field.

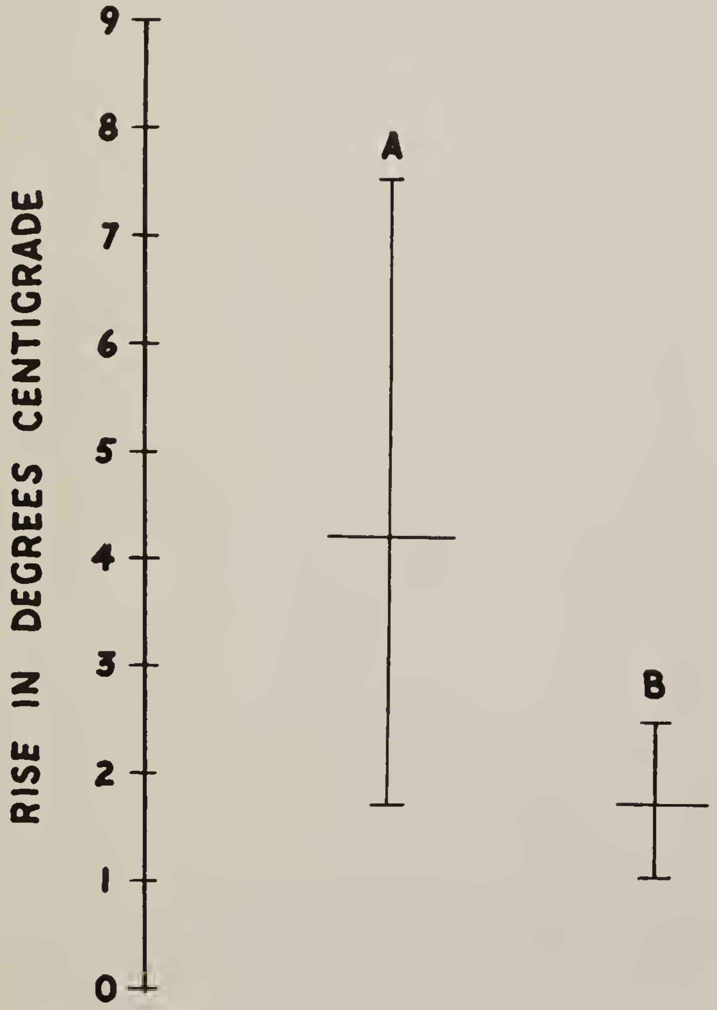

Fig. 4.—Graph showing temperature increments in colon: A) Full. B) Empty.

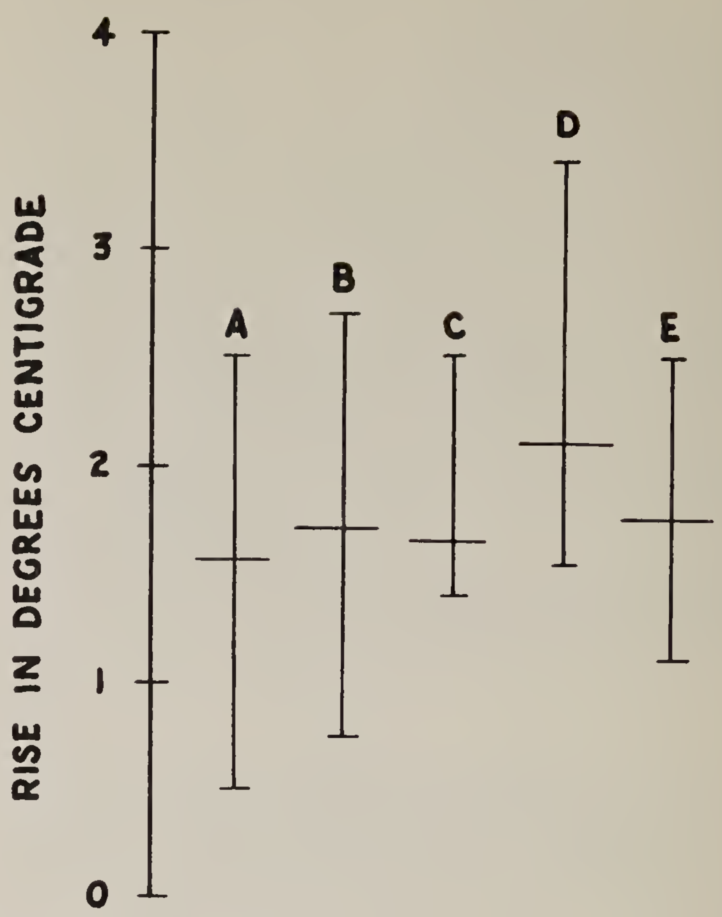

Fig. 5.—Graph showing similarity of temperature increments in A) Liver; B) Spleen; C) Kidney; D) Empty stomach; E) Empty Colon.

DISCUSSION

From these experiments it is apparent that gastrointestinal contents are responsible for the marked rise in temperature in the stomach and colon of rabbits irrespective of diet.

There are three types of electrical response producing heat in an electromagnetic field: 1) Dielectric loss. 2) Hysteresis and 3) Eddy current. A detailed analysis of the gastric contents of Rabbit 433 immediately following a final control run showing that no magnetic substances were present, is appended. (Tab. 1) As a magnetic substance is necessary for hystereis heating to occur, this form of heating may be excluded. Dielectric heating occurs in any substance which is not a good electrical conductor when in an electromagnetic field. Since the substances found in the gastric contents analysis are all good to fair conductors and the frequency employed in these experiments (120 Kc) produced only 1/10,000 the heating of an ordinary diathermy machine, it seems unlikely that dielectric heating is responsible for the heating effects in these experiments. Eddy current heating occurs in conductive material in an electromagnetic field. Analysis of the gastric contents revealed this type of material. Detailed experiments, to be reported, show that the heating effect in the stomach is dependent on mass and surface area relationships which are a characteristic of eddy current heating. While no studies have been carried out on human beings by us in this field, the pathology in the bowel due to the rise in temperature of its contents is similar to that reported in man on one occasion and must be further investigated when larger coils are made available for use on human subjects.

TABLE 1

ANALYSIS REPORT OF STOMACH CONTENTS OF RABBIT #443

Total Weight	97.9	gm.
H_2O	87.2	gm.
Dry Solids	10.7	gm.
Ash	1.17	gm.
Na in ash	0.053	gm.
K in ash	0.090	gm.
Cl in ash	0.162	gm.
Free HCL	0.063	gm.
Volatile Solids	9.50	gm.
Total H^+	8.96	meq.
Free HCL	1.74	meq.
p^H	2.40	

Ash contained a large fraction of acid insoluble material, presumably silica in form of silicates.

SUMMARY AND CONCLUSIONS

We have tested the effect of emptying the gastrointestinal tract by starvation on the M.L.D.$_{50}$ of rabbits before exposure to an electromagnetic field. Starvation for eight days caused the M.L.D.$_{50}$ to rise from 6 minutes to 20 minutes. This was attributed to elimination of the effects of eddy current heating produced by the presence of intestinal contents.

Following the above work a larger 15 inch coil was constructed producing 15,000,000 volt ampers across the coil to achieve a 500 oersted field. This coil operates at 55 Kc. to achieve a greater depth of penetration. Work is now in progress in studying the effects of radiation alone on bone marrow, plasma proteins and the effect of selective heating of the liver and stomach from the physiological and pathological view point in dogs.

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MITHRAMYCIN IN THE TREATMENT OF DISSEMINATED CANCER

A Preliminary Report

SYDNEY KOFMAN, M.D.
NORMAN REAM, M.D.

It would seem that any cancer chemotherapeutic compound which is capable of producing a complete tumor regression is worthy of extensive clinical trials in other forms of human cancer. In 1961, we observed the effects of mithramycin (PA-144) on three patients with metastatic testicular tumors. Each patient had rapidly growing pulmonary metastases. Two patients did not respond to mithramycin; the third patient had a dramatic and rapid regression with complete disappearance of pulmonary metastases. The tumor was an embryonal carcinoma which had not responded to the combination of methotrexate, chlorambucil and Actinomycin D given in combination as recommended by Li for metastatic testicular tumors.[1] The regression has continued for over nine months.

In 1960, Curreri and Ansfield presented a preliminary report on 36 patients treated with mithramycin.[2] In this report it was noted that mithramycin was toxic and that it was to be employed cautiously and with judgment. The therapeutic effects suggested continued evaluation of this compound in embryonal cell carcinoma of the testis, male choriocarcinoma, Wilms' tumor, and carcinoma of the breast. The same year, Parker et al reported on 19 patients with malignant solid tumors who had been treated with mithramycin.[3] They concluded that the drug produced marked subjective and objective toxicity and stated that it was not an effective antitumor agent in the dosage used. They also concluded that increases in dosage would probably produce more side effects.

Following these reports, clinical trials with mithramycin were sporadic and only a very limited supply of the antibiotic was available for clinical investigation. Review of the experimental work with mithramycin indicated that there had been a limited trial in many forms of disseminated cancer. A number of the patients treated were preterminal and the dose used was experimental and often toxic.

In June, 1962, a protocol was outlined to re-evaluate mithramycin in a variety of disseminated carcinomas.* The following is a preliminary report on 35 patients with disseminated cancer who were treated with mithramycin.

METHOD

Thirty-five patients with evidence of progressive metastatic disease were admitted to this study. Most of these patients were refractory to the more usual forms of cancer chemotherapy. A number of patients are still under study. The 35 patients included five patients with metastatic testicular tumors, (three embryonal carcinomas and two malignant teratomas with mixed elements), 15 pa-

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From the Section of Oncology, Department of Medicine.
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*Additional medication was obtained through the cooperation of Dr. Theodore J. Medrek from the John L. Smith Memorial for Cancer Research, Chas. Pfizer & Co., Inc., Maywood, New Jersey.

tients with metastatic carcinoma of the breast, four patients with systemic malignant lymphomas (two patients with Hodgkin's disease and two patients with lymphosarcoma), and eleven patients with a variety of other metatastic cancers. The detailed histology of the testicular tumors will be discussed at a later date. The predominant site of metastases in 11 of the 15 patients with disseminated carcinoma of the breast was visceral. The other patients had advanced soft tissue and/or osseous metastases.

Initially, two dosage schedules were employed. Schedule A: Patients received 50 micrograms of mithramycin per kilogram intravenously per day for five days. Schedule B: Patients received daily increments of mithramycin until the point of toxicity. The initial dosage level was started at 0.20 micrograms per kilogram per day and was increased by 0.05 micrograms per kilogram per day until the point of toxicity. When this was reached, the dose was then decreased to the level below that of toxicity. An attempt was made to treat the patient with a total dosage of between 150 and 250 micrograms per kilogram as a course of therapy.

OBSERVATIONS

Metastatic Testicular Tumors: Objective tumor regression occurred in two of the five patients. The tumor in each case was an embryonal carcinoma. Figure 1 illustrates the regression in a 30 year old male who had rapidly-advancing pulmonary and abdominal metastases. Combination therapy had failed to control the growth of the tumors. Mithramycin was started on February 22, 1962, and by April 22, 1962, there was almost a complete regression of the tumors. Since that time there has been a complete disappearance of all the metastases. The regression has continued for over nine months. The patient has been asymptomatic and has worked full time.

The second regression has been less dramatic. The patient, a 16 year old male, was first seen with advanced disease. He had a huge testicular tumor with extensive pulmonary and abdominal me-

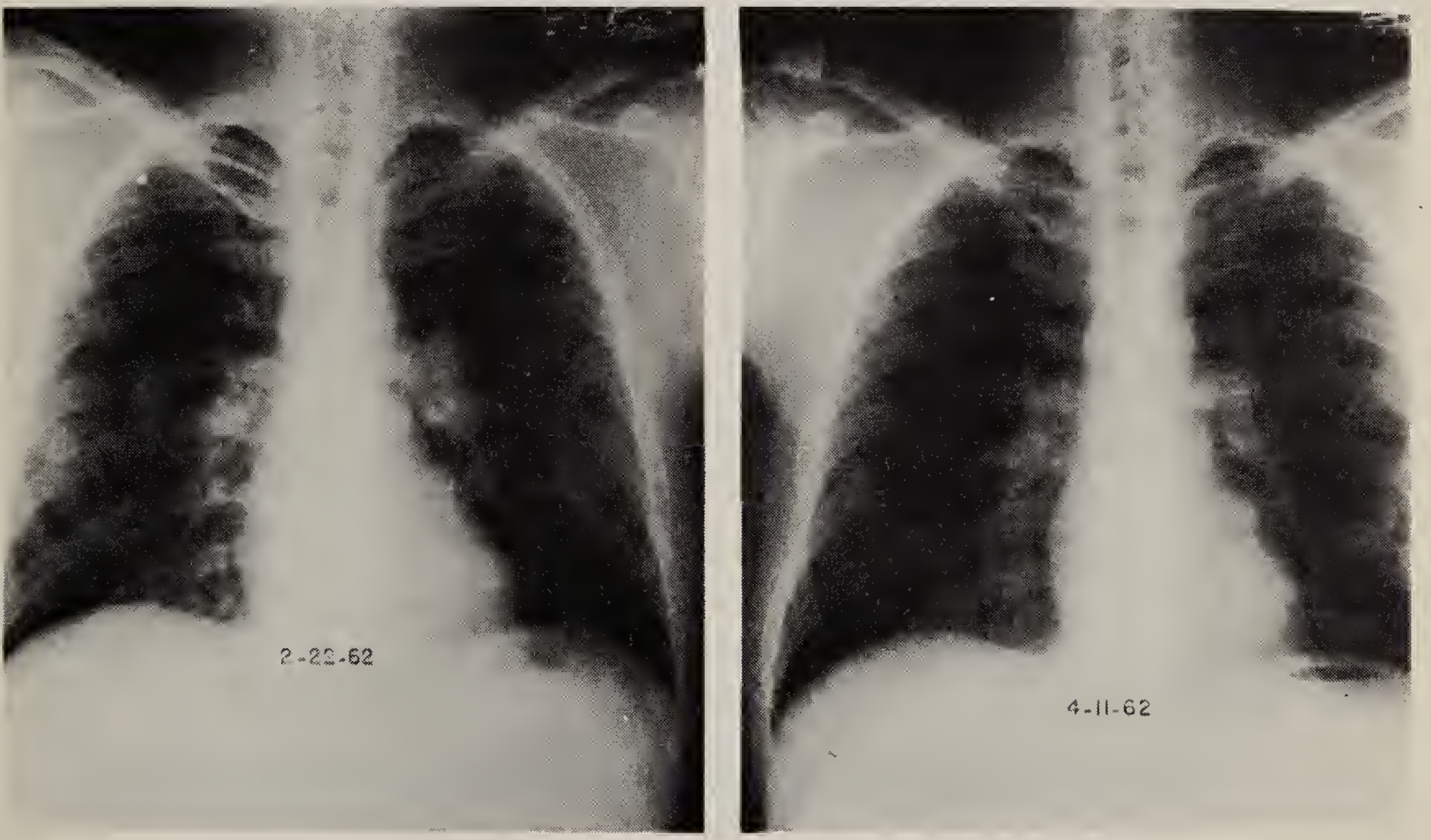

Fig. 1 Illustrates the regression in pulmonary metastases in a 30 year old man with metastases from an embryonal carcinoma of the testes. After a 25 day course or chlorambucil, methotrexate and actinomycin D the metastases continued to grow. Mithramycin was started several weeks later (2-22-62). By 4-22-62 the patient had received two courses of mithramycin. Since 4-22-62 the metastases have regressed completely.

tastases. Mithramycin produced a shrinkage in the small coin-like lesions but did not effect the size of the large lesions. Maintenance of the regression has been difficult because of the advanced state of the disease and because of the toxicity associated with mithramycin.

Four patients have been treated with combination therapy. This therapy had been given to three patients prior to mithramycin. Partial objective tumor regression had been noted in the two patients with malignant teratomas. These regressions lasted several weeks and additional therapy to the point of toxicity failed to maintain the regressions.

Disseminated Carcinoma of the Breast: Fourteen of the fifteen patients admitted to the study were evaluated. The fifteenth patient expired from a cerebral vascular accident during therapy. Ten of the fourteen patients had advanced visceral disease. The predominant site of visceral metastases involved the central nervous system in six patients, the liver in three, and the lung in one. Two of the other four patients had massive tumor invasion of the breast. The third patient had a rapidly-advancing inflammatory carcinoma and the other patient had bilateral pleural effusion, with widespread osseous metastases.

Ten of the fourteen patients had received hormone therapy; only two responded. Both patients had extensive visceral metastases which were progressing at the time mithramycin was started.

Four patients were treated with 5-fluorouracil and the tumor continued to grow in each patient.

Two patients had spinal cord metastases. Each patient responded to therapy. Figure 2 illustrates the spinal fluid levels of protein and lactic dehydrogenase before and during mithramycin therapy in a 67 year old lady with disseminated carcinoma of the breast. She had an ini-

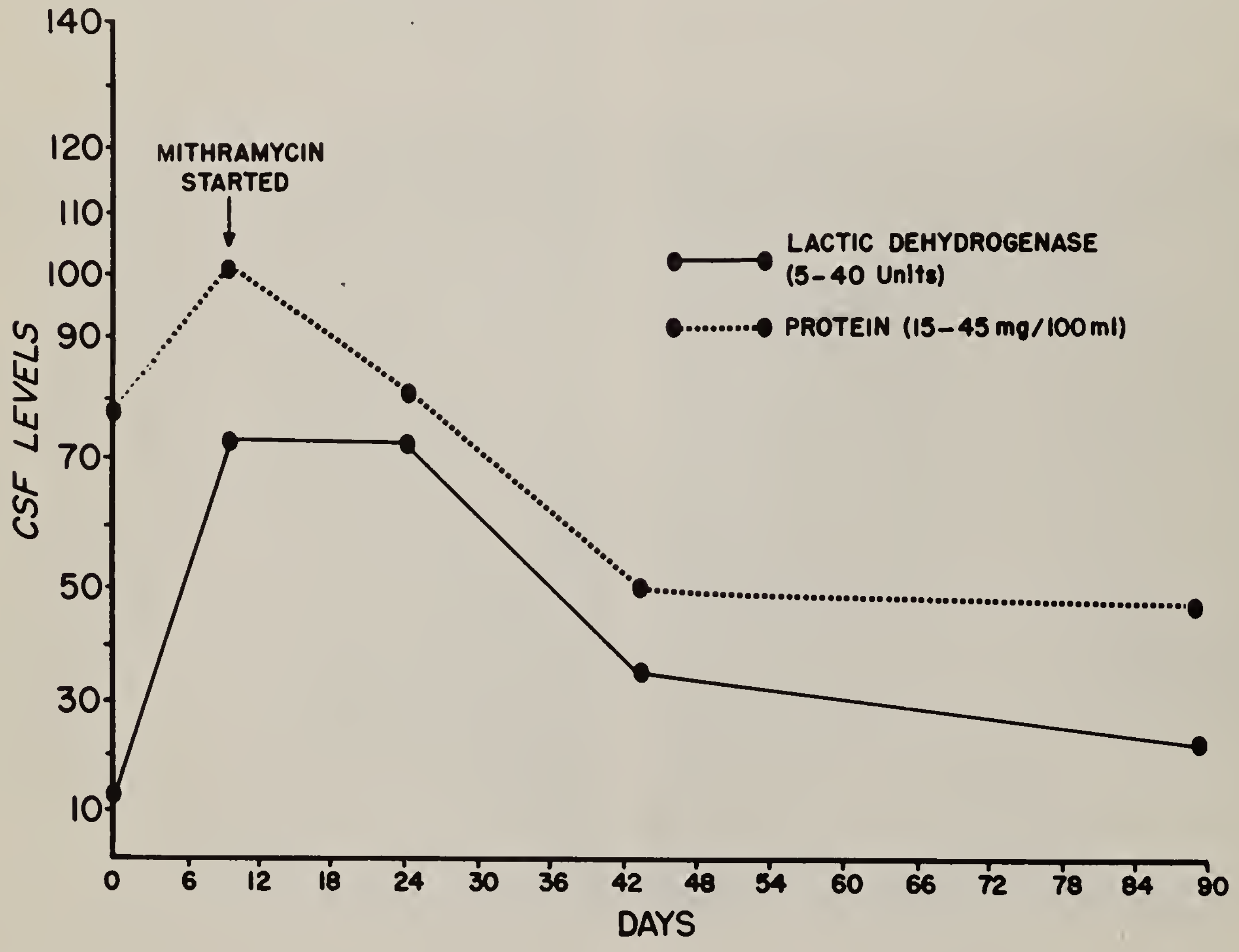

Fig. 2 Illustrates the spinal fluid levels of protein and lactic dehydrogenase before and during mithramycin therapy. Clinical improvement preceded the changes in the spinal fluid chemistries and has continued more than three months after starting mithramycin. There appears to be a difference in the dose required to control CNS and osseous metastases in that the patient has required supplementary radiation for bone metastases.

tial regression of pulmonary metastases with estrogen and when her disease progressed, corticosteroids later followed by androgens were ineffective. Clinical improvement with mithramycin was rapid and preceded the improvement in spinal fluid chemistries. The patient had been bedridden with pain, requiring morphine and there was numbness and difficulty in opening the left hand. At the present she is ambulatory and able to use her hand normally. Regression of hepatic metastases was also seen in this patient. Supplementary radiation therapy to the right femur was required to control pain from bone metastases.

The second patient is a 48 year old Negress who had had a hypophysectomy for disseminated carcinoma of the breast. The disease continued to progress following the hypophysectomy and intermittent radiation therapy was required to control pain. In June, 1962, severe back pain and sciatica occurred and the patient was bedridden. Large doses of corticosteroids, later followed by a course of 5-fluorouracil did not improve the patient. Mithramycin was started in July, 1962. This resulted in decrease in pain and control of neurological symptoms. The patient has required intermittent mithramycin therapy and the tumor has been under control for four months.

Clinical improvement occurred in two of the four patients with cerebral metastases. Figure 3 illustrates the control of cerebellar ataxia in a 50 year old woman with cerebellar metastases. At first there was a rapid disappearance of headaches and nausea, but continued therapy with mithramycin appeared to exacerbate these symptoms. Because of this corticosteroids were added. However, the clinical improvement could not be maintained and the patient died from a herniation as the result of cerebral edema. The improvement in the other patient was less remarkable and transient.

Objective regression of soft tissue metastases occurred in three patients. The regression has been maintained in one patient for three months. The second patient had rapidly progressing skin and subcutaneous nodules which appeared inflammatory. Treatment with mithramycin produced a regression of these tumors which lasted four weeks. Because of moderate toxicity additional mithramycin therapy has been withheld. The tumors have failed to respond to estrogens

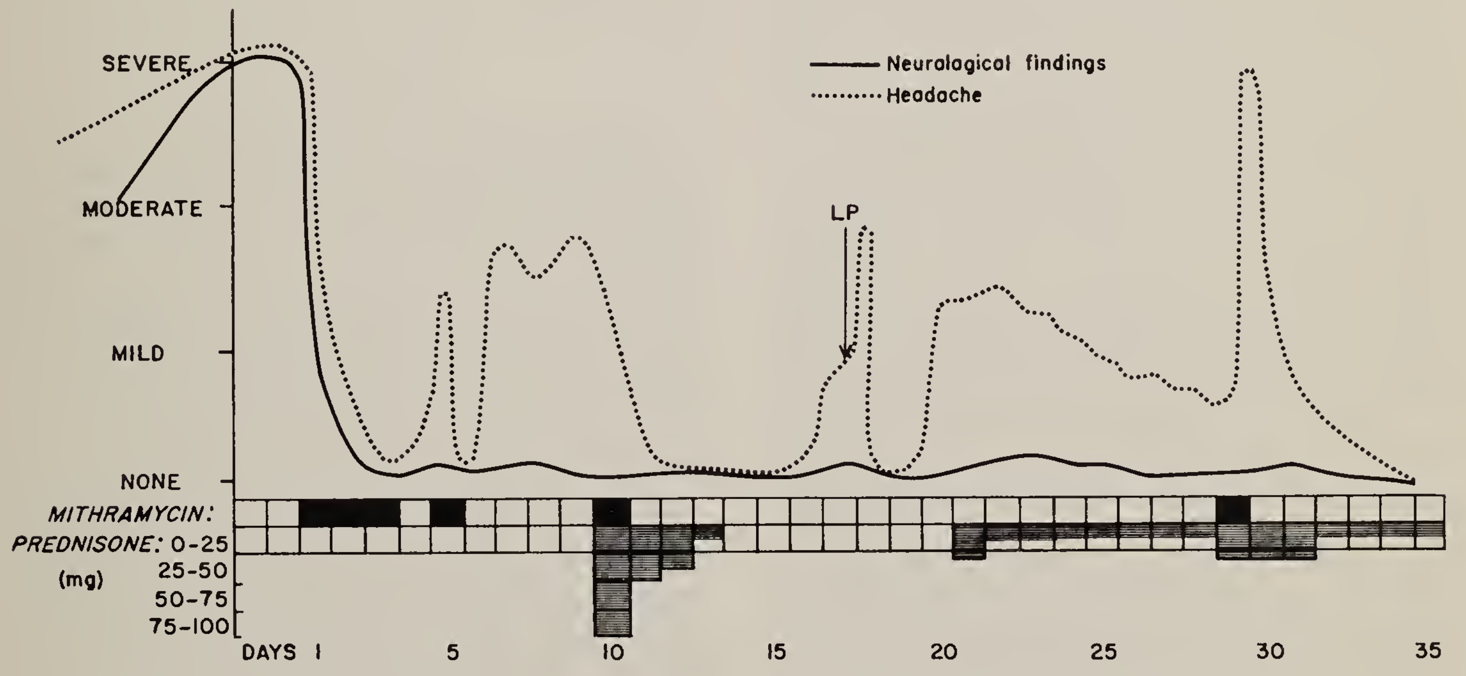

Fig. 3 Illustrates the control of cerebellar ataxia in a 50 year old woman with cerebellar metastases from carcinoma of the breast. The improvement was rapid and dramatic. Because of cerebral edema, the dose of mithramycin was limited. Corticosteroids were of value in controlling temporarily the cerebral edema.

and at present the patient is receiving androgens. A fifty percent reduction of soft tissue metastases was seen within four weeks in the third patient. At the onset of therapy the patient had been jaundiced and had a huge liver with poor liver function. Initially, the serum bilirubin decreased. However, therapy was limited by the advanced liver disease and the patient expired as a result of hepatic failure.

MALIGNANT LYMPHOMAS: Decrease in size of tumors was seen in both patients with Hodgkin's disease. One of the patients is a 24 year old male who had bilateral pulmonary infiltrates. His identical twin had expired as a result of pulmonary failure from advanced parenchymal infiltration. Chlorambucil, cyclophosphamide, and vinblastine sulfate had been ineffective in the identical twin. Because of this it was decided to try mithramycin. The first course of therapy resulted in a 15 to 25 percent decrease in size of the pulmonary infiltrates. The regression lasted four weeks and a second course of therapy produced a similar regression.

The other patient had advanced Hodgkin's disease when mithramycin was started. Cyclophosphamide had been ineffective. Mithramycin produced a transient decrease in size of the cervical and mediastinal nodes. Patient became afebrile during the therapy. Although the decrease in size of the nodes was minimal, the change was measurable readily.

One of the two patients with lymphosarcoma had a regression with mithramycin. This patient is a 62 year old lady who had fever, hemolytic anemia, and enlarged retroperitoneal nodes. Previous therapy had consisted of intermittent radiation, small doses of corticosteroids and chlorambucil. The chlorambucil had been discontinued because of nausea and vomiting. During therapy with mithramycin the patient became afebrile and there was a 25 percent decrease in size of the retroperitoneal nodes, as demonstrated on a lymphangiogram.

MISCELLANEOUS TUMORS: Eleven patients with a variety of other tumors were treated with mithramycin. Tumor regression was seen in one patient. This patient had widespread metastases from a carcinoma of the stomach. The first course of therapy produced a decrease in size of the tumors, coincident with symptomatic improvement. The regression lasted three weeks. A second course of therapy has resulted also in tumor shrinkage.

TOXICITY

The side effects associated with mithramycin have limited the effectiveness of therapy. The most common side effects include anorexia, nausea, vomiting, headaches, drowsiness, fever, and muscle aches. Thrombocytopenia and hemorrhage have been seen on occasion. Hepatic failure was seen in the patient with extensive hepatic metastases. Hepatic and renal toxicity have been reported previously and usually occurred with large doses of mithramycin.[2,3]

Individuals have shown a wide range of sensitivity to mithramycin. Schedule A (50 micrograms per kilogram per day for five days) was too toxic for some patients. Schedule B, although less so, was still toxic. Because of this, other schedules, including 24-hour infusions, are being evaluated.

DISCUSSION

Mithramycin, an experimental antitumor compound, is an antibiotic derived from Actinomycete culture belonging to the genus Streptomyces. Its formula and mechanism of action are unknown. The side effects of mithramycin have limited its therapeutic value and a number of patients in this study were unable to receive a full course of therapy.

Despite this, mithramycin appears to have an important role in the treatment of metastatic embryonal carcinoma of the testis. The longest regression continues more than three years following mithramycin therapy.[2] In the same study, Curreri and Ansfield commented on a second patient who had a dramatic regression in pulmonary metastases. Unfortunately, this patient developed a lung abscess three months later and died suddenly from aspiration. The importance of mithramycin in these tumors is emphasized in this study by the observation of a complete regression of pulmonary and abdominal metastases in a patient who had not responded to combination therapy. Although sensitivity to a drug is the most important factor in determining the responsiveness of the tumor, there is evidence that failure in some of the patients may have been due to the advanced state of the disease at the time mithramycin therapy was started.

The role of mithramycin in the treatment of disseminated carcinoma of the breast is less clear. We have already many agents which are effective in this disease. Further experimental work with mithramycin is indicated since tumor regressions were seen in some patients with breast carcinoma who were unresponsive to other forms of therapy. In addition, most of the patients treated had advanced metastatic disease which was unresponsive to conventional forms of therapy. Although transient shrinkage of soft tissue tumors in terminal patients is of little value to the patients, such observations are worth noting for experimental purposes, and suggest that worthwhile regression might occur if there were a better selection of patients.

The clinical improvement noted in patients with central nervous system metastases from the breast is important, especially since other therapy had been ineffective. In the past, corticosteroids have been the only chemical agents which have controlled symptoms due to central nervous system metastases with any degree of frequency.[4] In most cases, the improvement with corticosteroids appeared to be due to reduction of edema and inflammation surrounding the tumor cells. The mechanism of action of mithramycin is probably more specific. One of the limiting factors with mithramycin has been the temporary exacerbations of symptoms noted during therapy in the patients showing clinical improvement. This may be due to edema occurring secondary to tumor cell necrosis. In one patient corticosteroids helped control the edema temporarily. Corticosteroids were not required in the two patients who have had a more prolonged control of their central nervous system metastases.

Since the brain and spinal cord are within a rigid enclosed cavity, relatively minor reductions in the size of a mass or surrounding edema may be sufficient to produce major symptomatic relief. It is surprising that other compounds have not been more effective. Becaue the levels of mithramycin are so low, measurements in blood and spinal fluid have been difficult. The improvement in the neurological picture and the neurotoxicity associated with the drug indicate that a significant amount of the antibiotic crosses the blood brain barrier.

Additional trials in other metastatic tumors to the central nervous system, as well as in primary inoperable tumors, are indicated. Corticosteroids have produced clinical improvement even in tumors which are generally unresponsive to these hormones, emphasizing their nonspecific action. On the other hand, there is evidence that mithramycin produces improvement only in those patients who have responsive tumors.

The role of mithramycin in the treatment of malignant lymphomas has not been established. We have many agents which are effective in these tumors. Additional evaluation of mithramycin in malignant lymphomas is indicated and should not be reserved for terminal patients. Since mithramycin does not produce a significant leukopenia, it may be of value, either alone or in combination with corticosteroids, in the treatment of patients with malignant lymphomas associated with leukopenia. The value of corticosteroids in the treatment of malignant lymphoma has been reported previously.[5,6] It may be important also in the treatment of patients with central nervous system disease.

Severe nausea, vomiting, headache and drowsiness have been the major factors which have limited therapy with mithramycin. Many of the side effects appear to be due to the effect on the central nervous system. Reduction in side effects has been noted by giving divided daily doses. Curreri and Ansfield had tried three-hour infusions without a significant decrease in side effects.[2] In this study 24-hour infusions have been used in several patients and although the side effects persist, they are less drastic. We have been able to give larger doses of mithramycin over a shorter period of time with the 24-hour infusion. Further studies are underway to evaluate the effectiveness of this administration.

SUMMARY AND CONCLUSIONS

Mithramycin is an experimental antitumor compound. Its range of effectiveness against a variety of human tumors is being evaluated. It appears to cross the blood brain barrier and has produced clinical improvement in patients with central nervous system metastases from carcinoma of the breast. Regressions have been seen in patients with metastatic testicular tumors, disseminated carcinoma of the breast, carcinoma of the stomach and malignant lymphomas.

We wish to acknowledge most gratefully the efforts of Doctor L. W. Avery and Doctor John S. Garvin in helping evaluate the patients with central nervous system metastases.

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INTESTINAL MUCOSAL CHANGES INDUCED BY CHEMICAL CARCINOGENS

Raymond E. Anderson, M.D.
Willis G. Diffenbaugh, M.D.
E. Lee Strohl, M.D.
Wendell Schmidtke, M.D.

There is a great need, in the over all study of adenocarcinoma of the intestinal tract, for an available experimentally induced tumor that may be obtained in a predictable manner ([1, 8]). Although many gastrointestinal neoplasms have been developed by means of both chemical and radiation stimulation, the lesions so obtained have been observed to occur in a very haphazard fashion as to location, configuration, and incidence ([6, 7]). This, of course, has detracted from their general value, because it is almost impossible to study critically the natural history of this type of carcinoma as well as being difficult to sustain a uniform and reliable prototype lesion around which other studies may evolve. Furthermore, animals in which such tumors have been produced (mice, rats, guinea pigs, hamsters and rabbits) have been of a size which precludes accurate macroscopic study of the lesions so created. The surgical researcher whose primary interest lies in gross manipulation of cancer tissue or in the appraisal of various direct surgical, chemical, or radiation methods for its control or eradication must have available to him a working tumor in a larger laboratory animal.

While it is certainly not the ideal, the fact remains that the dog is the most commonly utilized larger experimental animal in the great majority of laboratories throughout the country, and will probably continue to be such for many years to come. Therefore, it seems reasonable at this time to appropriate this creature as the one in which induction of the desired lesion should be attempted. Previous investigators have failed to successfully induce canine intestinal adenocarcinoma and the reports of such work have been sketchy and infrequent[9]. No one has yet documented an intensive exploration of this area of carcinogenesis[3].

This report incorporates observations which have been made during the first fourteen months of an experiment in which chemical carcinogens of known potency have been applied to the intestinal mucosa in a group of laboratory dogs. It must be appreciated that this span of time is not of sufficient length to allow optimistic anticipation of malignant change. Early physical changes which do occur, however, appear to mimic those seen in the smaller laboratory animal[2,5] and probably represent a parallel evolution at this stage in their carcinogenic effect.

From the Department of Surgery
Aided by a Grant From the Illinois Division of the American Cancer Society.

METHODS OF THE EXPERIMENT

Two highly potent carcinogenic hydrocarbons were utilized in this phase of the experiment, 3-methylchlolanthrene and 7-12-dimethylbenzanthracene. The chemicals were loaded, in amounts of approximately 60 mgm., into gelatin capsules for implantation into the wall of the bowel.

Adult mongrel dogs were anesthetized with intravenous sodium nembutal. Under aseptic conditions, a lower midline incision was made and the abdomen entered. The colon was identified and mobilized into the wound. A 1 cm. incision was then made on the antimesenteric surface and by means of blunt dissection, both muscle layers were separated until the submucosal tissue prolapsed into this small incision. A dissector was then introduced 'at this level and a small pouch was developed in the adventitial tissue between the submucosa and circular muscle layers. A loaded capsule was introduced into this pouch for a distance of approximately 2 cm. The muscular layers were closed with a single fine black silk suture in order to prevent release of the chemical from the desired level. One to three implants were done in each dog. The abdominal wound was closed in layers using interrupted catgut sutures. The dogs were given a single injection of Combiotic (1.0 cc.) and returned to the open colony immediately.

A total of 19 implantations were undertaken in 8 animals. In 17 cases, 3-methylcholanthrene was the chemical of choice and in the other two, 7-12-dimethylbenzanthracene was used. At periods ranging from two to fourteen months, the animals were re-operated upon by the same technique as previously described. Attention was directed to the area of implantation, which was easily recognizable by the presence of the black silk suture. The entire area of implantation along with whatever reaction had occurred was completely excised and immediately fixed in formaldehyde solution. Sections were then routinely cut and stained by the hematoxylin and eosin technique.

RESULTS

Observations which were made on the sections are best described in chronological order, emphasizing the particular phenomena most commonly present at the biopsied stages between two and fourteen months. In four of the nineteen areas, more than one pathological change had occurred. However, only the major area of degeneration was recorded for this experiment. Namely, those changes which were considered as having been more advanced in each section were tallied as the main pathological alteration having taken place at the time of excision. Once again, it must be kept in mind that our observations represent the total effect of chemical carcinogenesis up to the time that excision was undertaken. What the eventual outcome of individual implants might have been over a longer period of time is only a matter of conjecture.

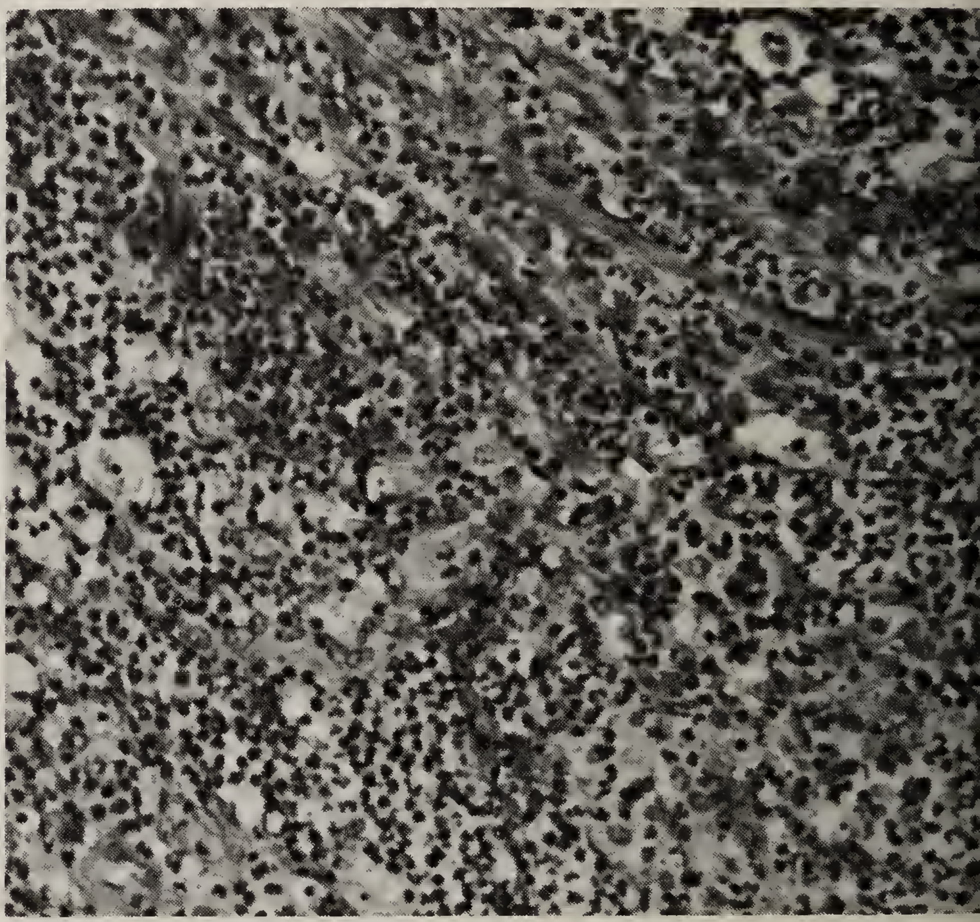

Fig. 1.—Abscess and Granuloma: This represents a typical reaction to the presence of 3-methylcholanthrene in the submucosal area after five months of implantation. The inflammatory and foreign body cells do not differ in any way from those seen in other types of necrosis.

A. Submucosal Abscess and Granuloma: (Fig. 1). Despite the fact that the chemical carcinogens are implanted aseptically, development of abscess and granuloma is a consistent finding within two to five months following their implantation. This appears to be the initial response to the caustic effects of the chemicals. While this in itself certainly does not involve carcinogenesis, it does reflect the primary response of the host to an active foreign body. The cellular profile in no way differs from that seen in the usual type of necrosis and reaction. As a matter of fact, the presence of inflammatory cells appears to be a consistent finding as long as eight and one-half months after the original application.

B. Perforation of the Muscularis Mucosa: (Fig. 2) While submucosal abscess or granuloma are not in themselves greatly important, perforation or ulceration of the muscularis mucosa permits contact of the carcinogens with the deep mucosal cells. This physical change has been observed at six and seven and one-half months after original implantation was carried out. Ivy[2], felt that this was an important stage in artificially induced tumors and has described the process as it occurred in the rabbit. Both 3-methylcholanthrene and 7-12-dimethylbenzanthracene will produce this type of ulceration, although 7-12-dimethylbenzanthracene appears to be somewhat slower in its effect.

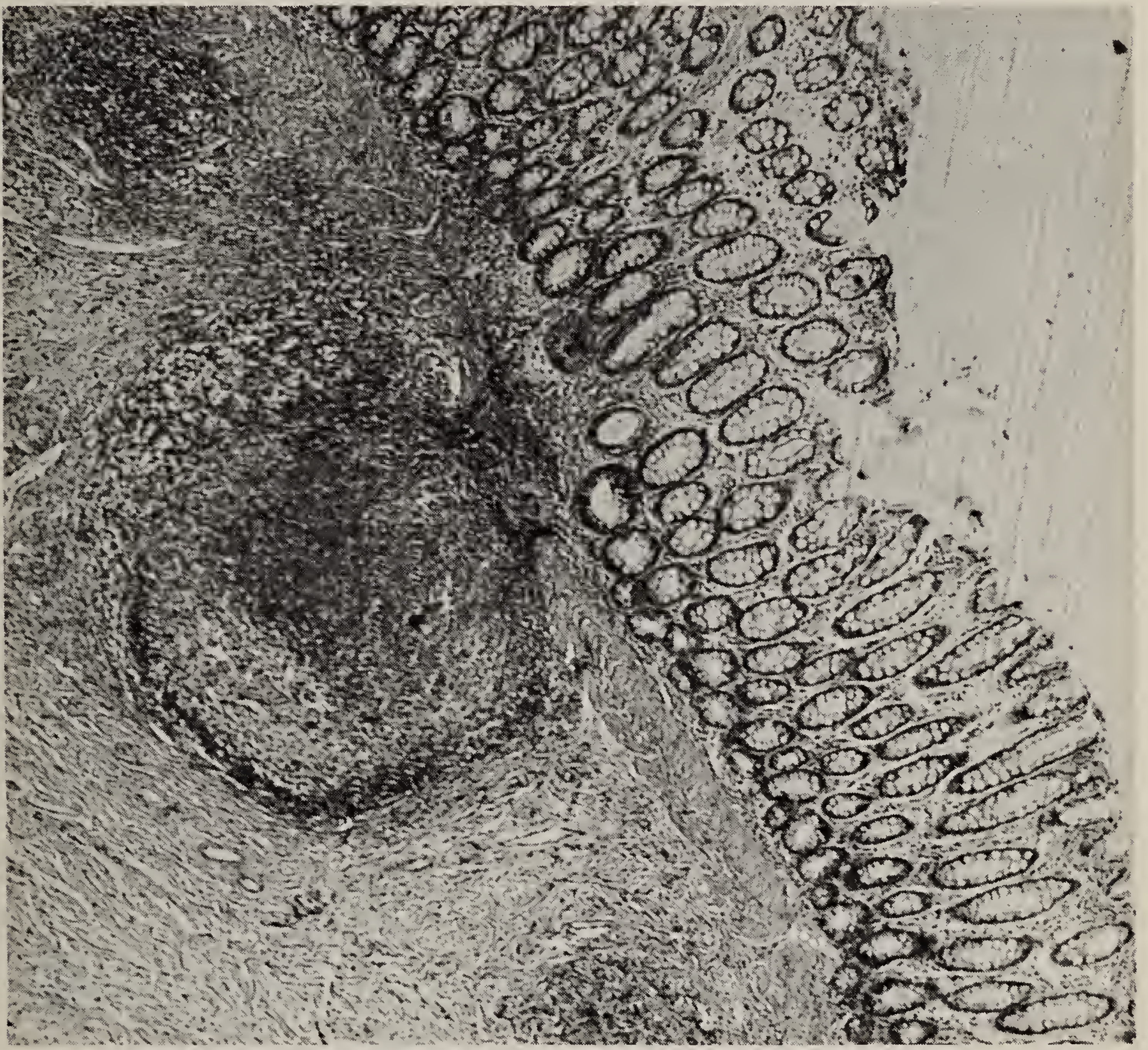

Fig. 2.—Perforation of the muscularis mucosa: This phase appears to be the first contact of the necrotizing chemical with the sensitive cells in the deep mucosal layer. This barrier having been overcome, progression has been observed to develop rapidly into the intestinal lumen. This biopsy was taken from an animal at five and one-half months.

C. Mucosal Ulceration: (Fig. 3) Between five and one-half months after implantation, a mucosal ulcer develops. The caustic effects of the chemical carcinogen appear to necrotize completely the mucosal cells, eventuating in an open luminal wound. The exact timing of this process is unpredictable and may depend both upon the depth of the initial implant and the amount of material used.

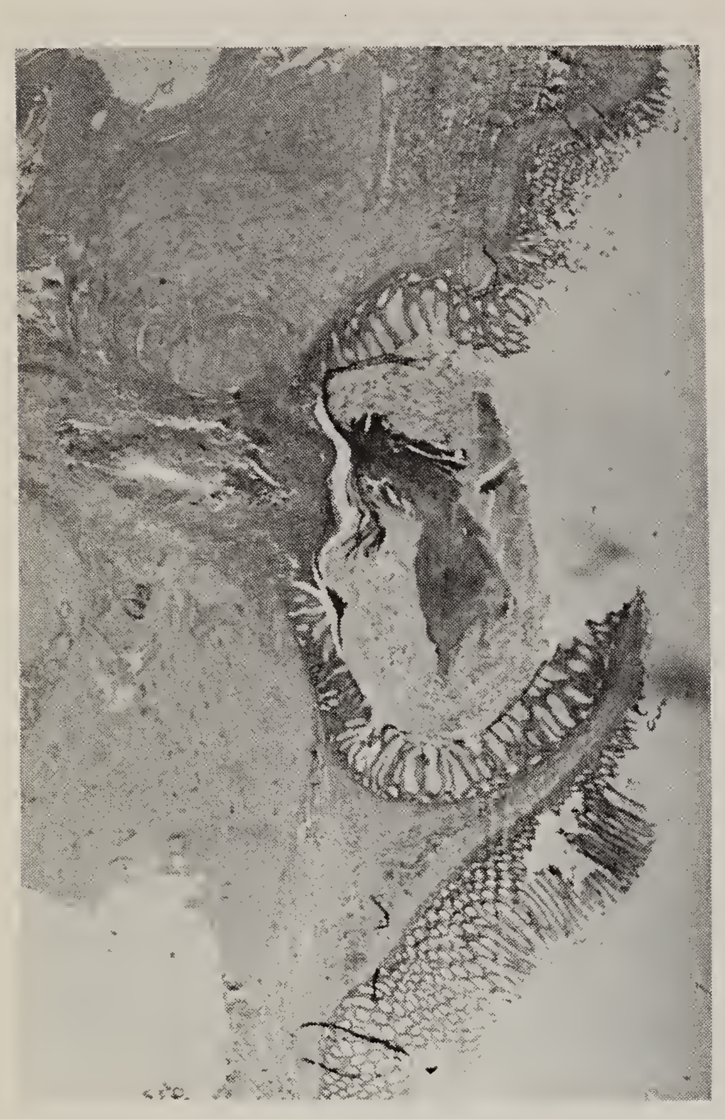

Fig. 3.—Mucosal Ulceration: Observation of this section reveals colonic ulceration which could be the result of any type of inflammatory process. The jagged edges and denuded base communicate with the scarred and granulomatous crater. There are no proliferative cells in the crypts, but the process appears to be a logical sequence to that which is observed in Figure 2.

D. Submucosal Scarring: (Fig. 4) The most commonly observed change at the point of implantation is an area of submucosal scarring. Fibroplastic reactions are observed in the periphery of most scarred areas, but the submucosal nodule of scar tissue is a relatively common finding. This reaction most likely represents a normal body reaction to the previous ulceration and inflammation.

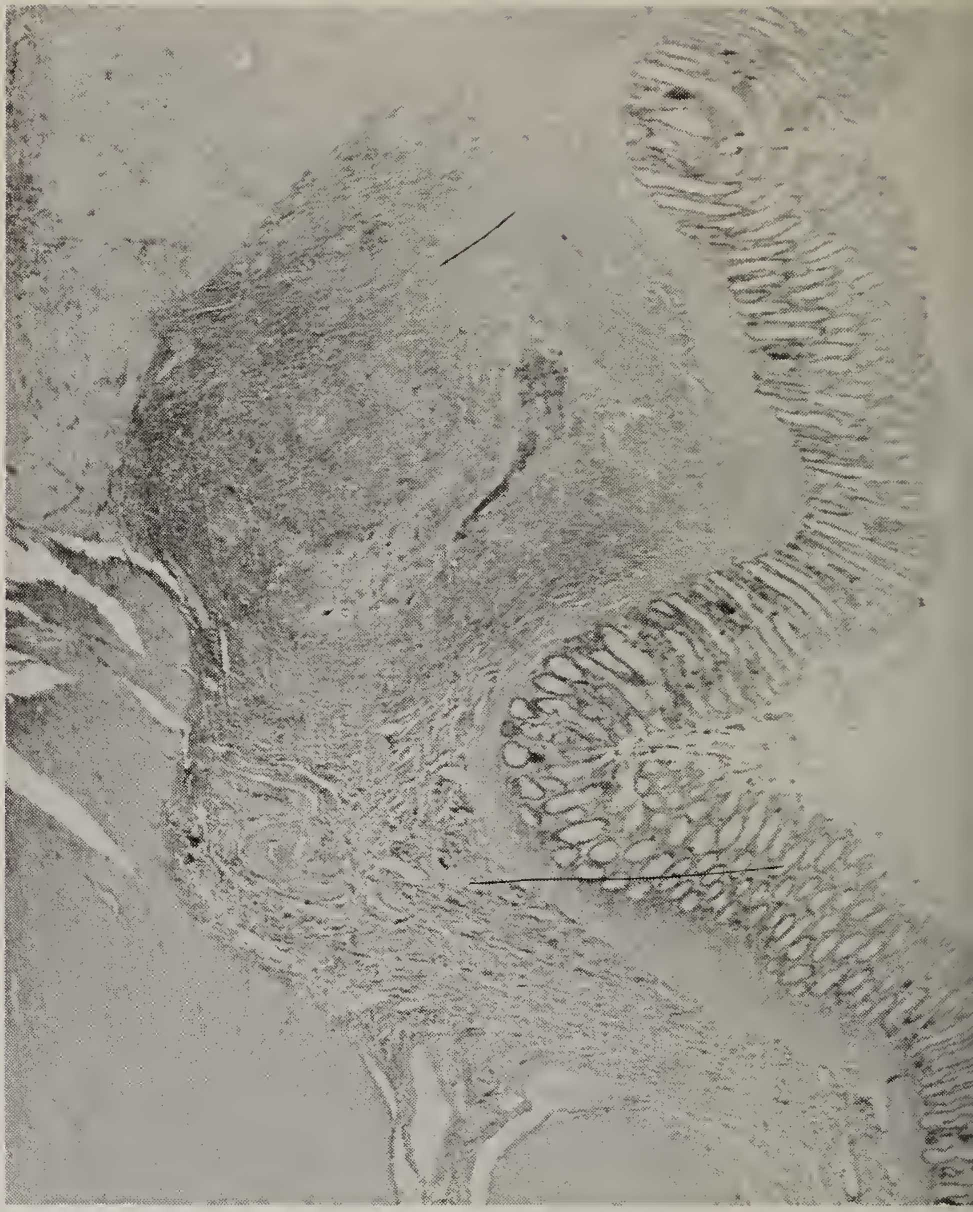

Fig. 4.—Submucosal Scarring: Nodules of hard and brawny scar tissue are the most common finding after a period of time at the site of implantation. Mucosal ulceration has apparently healed, and the gritty mass is all that remains of the implant. Inflammatory cells are still observed, but the normal process of healing is well on its way. This was biopsied at eight months after implantation.

E. Diverticulum Formation: (Fig. 5) As healing occurs, it is apparent that diverticula formation is common at the point approximate to the area of implanted chemical. The diverticulum is most likely a traction type and represents the end result of submucosal scarring. Other workers[4] have described diverticula in smaller animals subjected to the irritation of chemical carcinogens and once again it appears that the early mucosal changes seen in the dog may be akin to those which are known to occur in other laboratory animals.

F. Inclusions: (Fig. 6) The presence of small nests of cells in the submucosal tissue, consisting of irregular cystic masses

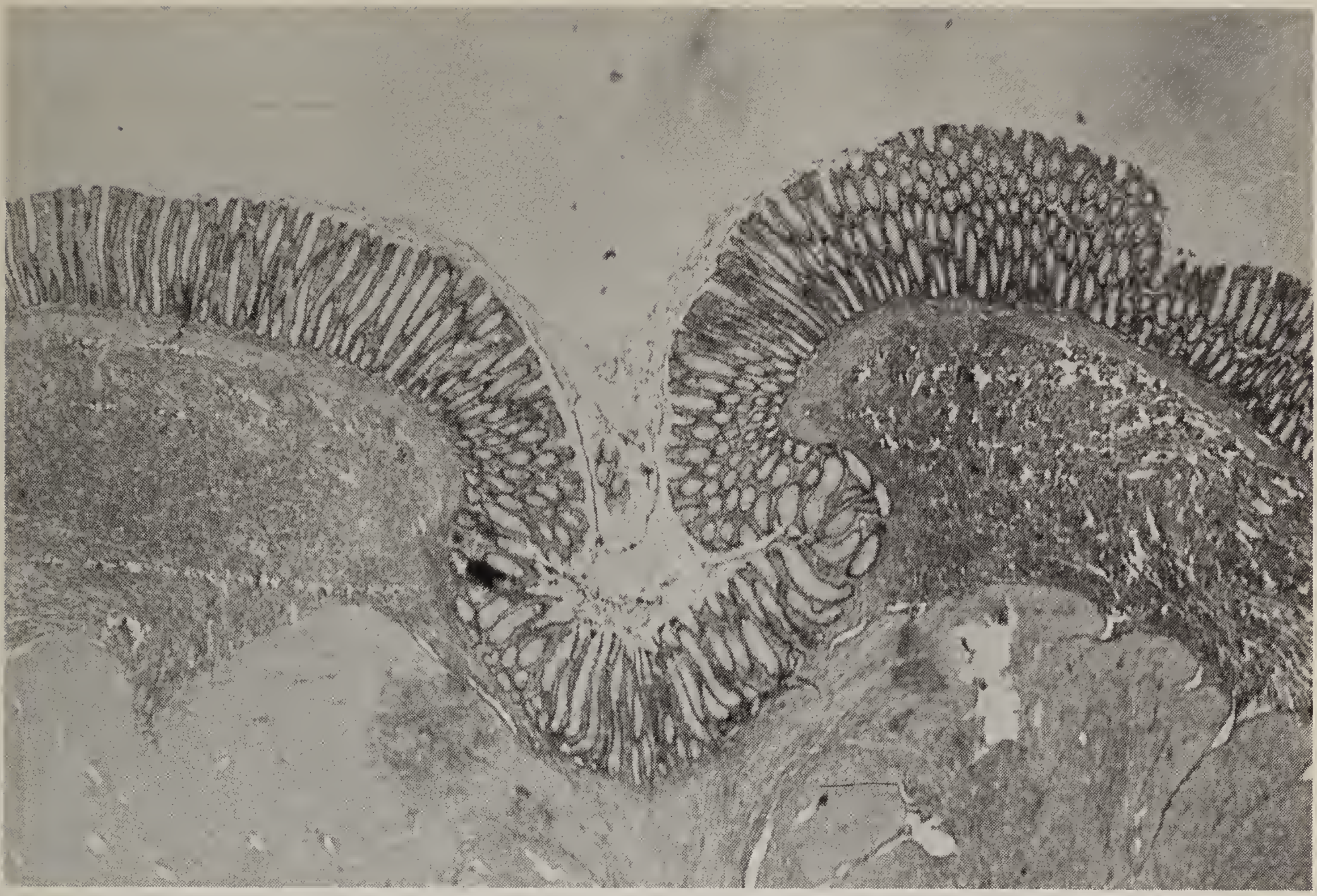

Fig. 5.—Diverticulum Formation: Dense scar tissue, developing at the point of insult, may retract the mucosal margin, with a resulting diverticulum formation. Although the mucosa appears to be intact, six animals demonstrated this finding, at periods ranging from four to fourteen months after implantation.

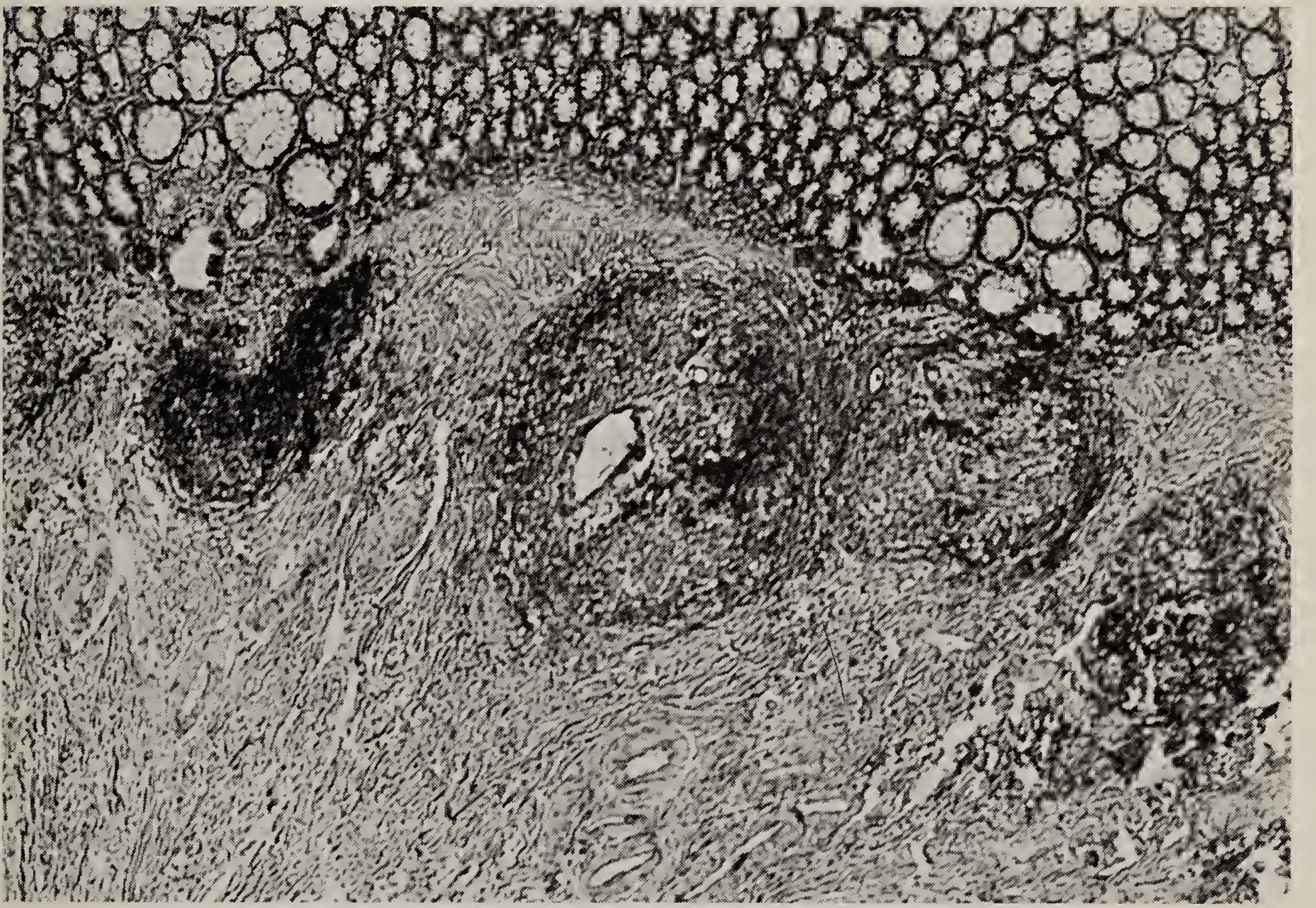

Fig. 6.—Inclusions: Healing of the muscularis mucosa has taken place, yet abnormal clusters of mucosal cells persist in the submucosal area at this biopsy, taken at 8 months in a dog implanted with 3-methylcholanthrene. Surrounding the cell nests are tightly organized inflammatory reactions; yet, the general appearance is that of a migration of mucosal cellular elements beyond their natural confines.

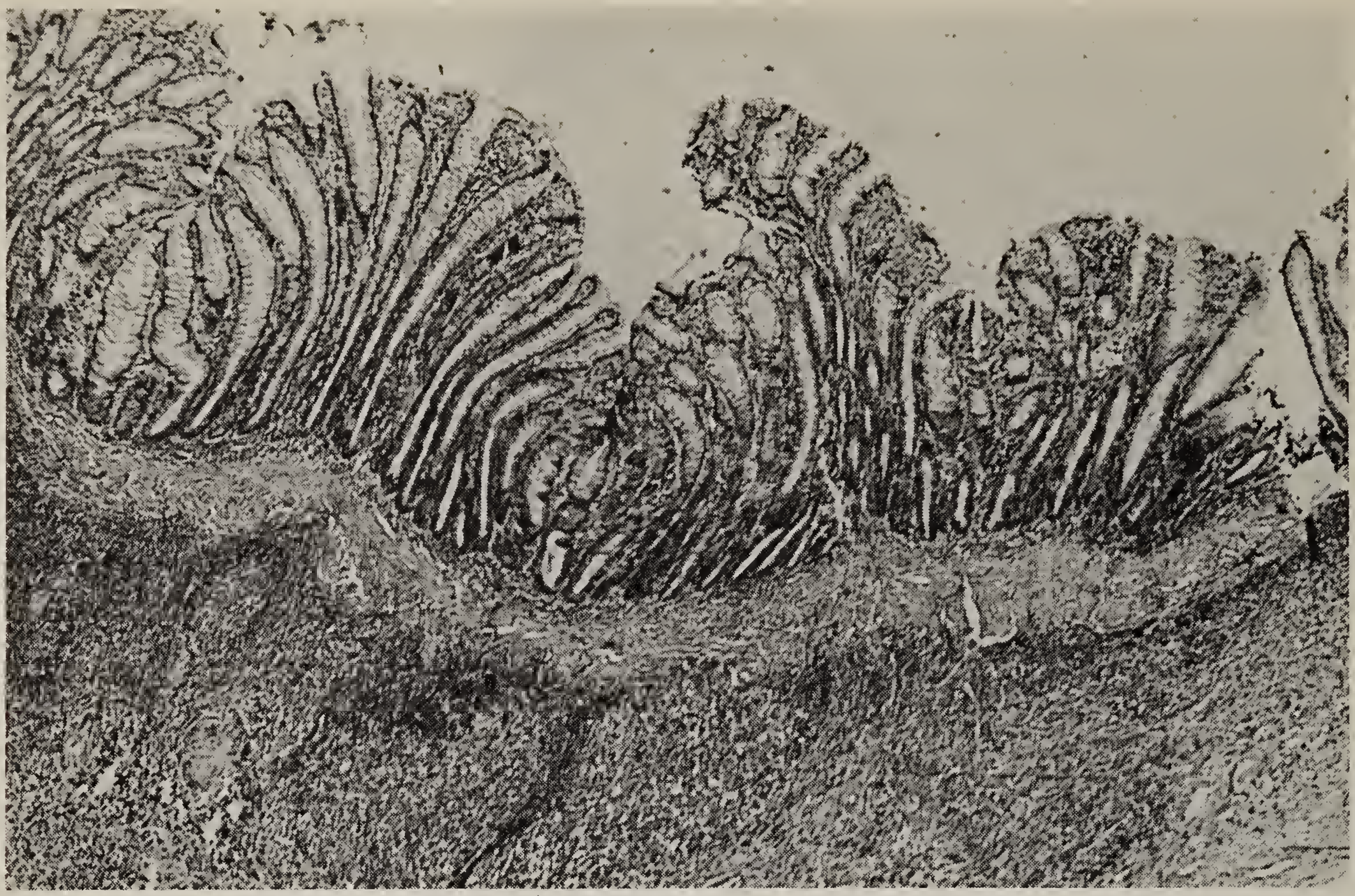

Fig. 7.—Polypoid Reaction: Gross observation of this lesion was that of a polyp, but the microscopic analysis must be restricted to that of "polypoid reaction." This animal was sacrificed after 8 months and its entire colon surveyed, without evidence of other abnormalities other than that at the site of implantation.

lined with mucosal epithelium, is one of the most interesting findings that we have thus far observed. The identification of these cells at this level is definitely abnormal and one is tempted to consider them to be of considerable importance in the natural history of chemically induced neoplasia. There is no way to tell, of course, whether nests of abnormal cells represent the persistent growth of mucosa, trapped beneath the muscularis layer after ulceration, diverticulum formation, and eventual scarring have occurred, but it is intensely interesting to note that these cells maintain their identity in an area quite independent of their normal position. The presence of inclusions was observed only once at a period of seven and one-half months.

G. Polypoid Reaction: (Fig. 7 and 8) The previous descriptions of pathological change have been those in submucosal areas, and most probably indicate direct response to the carcinogenic chemicals in contact with the cellular layers at this level of the bowel wall. The polypoid mucosal reaction was observed in an animal in which contact with 3-methylcholanthrene had been present for approximately eight and one-half months. We must assume that this pathological change represents stimulation or abnormal growth of the mucosal cells of the intestinal tract as a direct result of pure chemical irritation. While there is a great deal of controversy in respect to the relationship of polypoid formation to true neoplasia of a malignant type, it cannot be denied that adenomatous hyperplasia represents an abnormal growth pattern. Its presence at this relatively short interval of contact may offer some insight into the over all understanding of chemically induced adenocarcinoma of the canine intestinal tract.

H. Controls for the experiment were established by implanting a total of six unloaded capsules into the same type of submucosal pouch as was done with the carcinogenic hydrocarbons. The areas were studied at three and eight months and no evidence of foreign body reaction

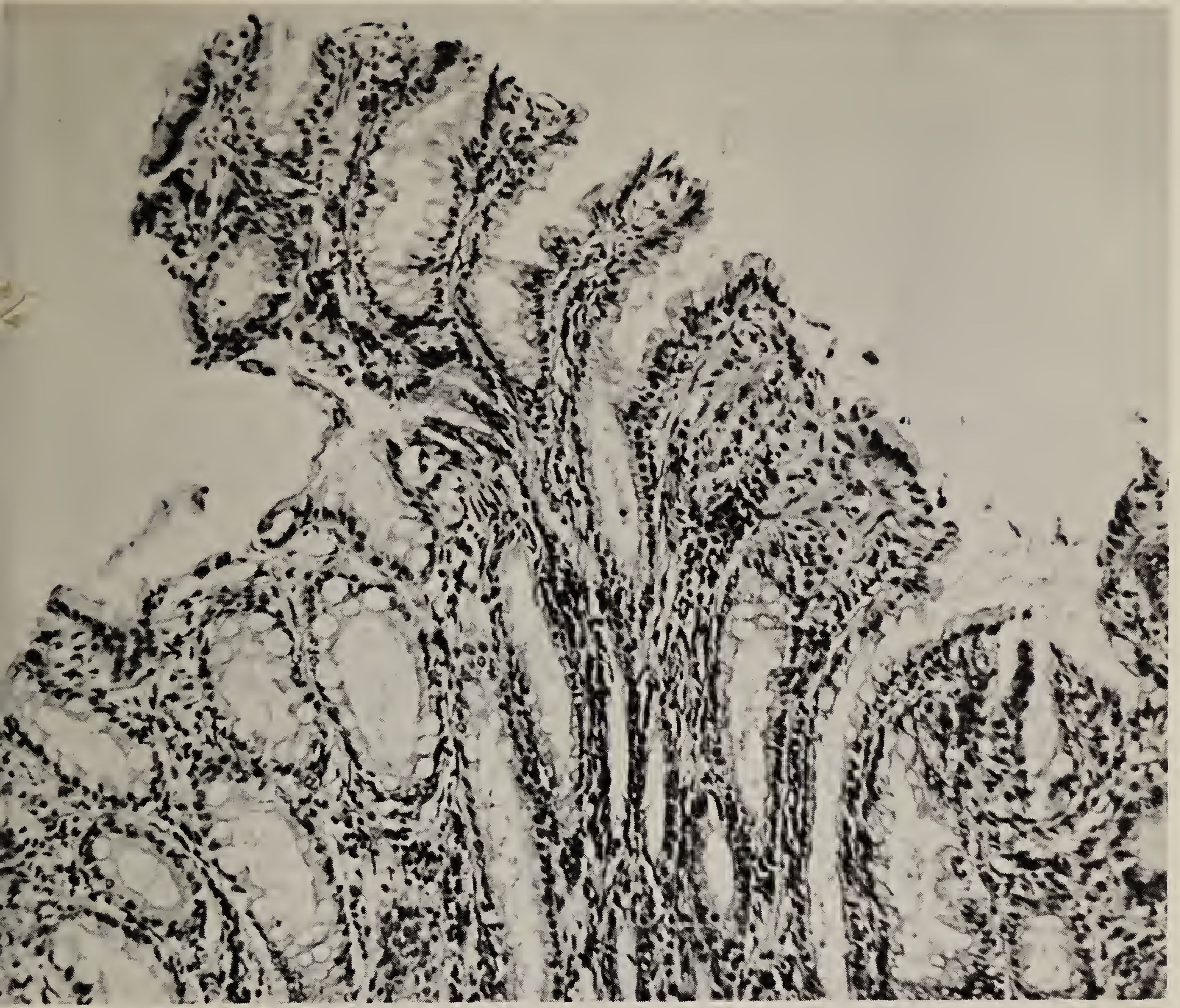

Fig. 8.—High Power of Polypoid Reaction: The cellular growth of this area under a higher magnification, confirms the diagnosis of a polypoid reaction in the mucosa above the area of carcinogenic implantation. The mucosal fronds are exuberant and the nuclei are hyperchromic and bizarre. There is, however, no true evidence of malignant degeneration in this section.

was noted. The black silk suture was found to be lightly encased in a filmy adhesion on the serosal surface of the bowel. Nodularity, mucosal deformity or visible evidence of defect was absent in each instance. Nevertheless, microscopic sections were taken from two of the control sites and in both of these, the minimal scarring that was observed represented only that of a normally healed postoperative wound. The areas, therefore, were recorded as negative.

SUMMARY

The need for an experimental prototype tumor of the gastrointestinal tract in a large experimental animal is apparent and urgent. However, such a working tool is not presently available to the investigator who is vitally interested in the surgical aspects of gastrointestinal malignant disease.

The absence of such a tumor, therefore, has been the challenge of this long term experiment in which carcinogenic hydrocarbons have been applied to the submucosal area of the canine colon in order to obtain microscopic and macroscopic observations which may eventually lead to the induction of a predictable and reproducable malignant neoplasm.

Observations on nineteen implantations of potent carcinogenic hydrocarbons has revealed that the early physical changes which occur may parallel those that are documented in the smaller laboratory animal.

Gross and microscopic assay of the chemical implantations have shown that the initial insult to the tissue results in necrosis, abscess formation and granulomatous change at the area of chemical contact with submucosal cells. A logical sequence of events during the ensuing seven to twelve months appears to be that of submucosal ulceration, mucosal cell destruction with open luminal ulcer, re-epithelialization, and the formation of submucosal scarring and diverticulum response, probably of the traction type, and possibly the trapping of mucosal cells beneath the submucosal layer as inclusions or mucosal nests in an abnormal position. Exuberant growth of the mucosal cells themselves was observed in a polypoid type of reaction in which excessive fronds of mucosa developed in an area directly in contact with the implanted chemical carcinogen.

We are indebted to Dr. Edwin Hirsh for his valuable assistance in the microscopic interpretation of the changes occurring at the sites of implant.

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NITRATE THERAPY IN EXPERIMENTAL CORONARY OCCLUSION

Robert N. Hedges Jr., M.D.
John M. Somerndike, M.D.

The ultimate goal of therapy in the acutely infarcted heart is to provide as much blood as possible to the total viable myocardium. It would seem that nitrates may be able to provide a time-honored therapeutic agent in this regard, as long as its limitations are not exceeded.

In a previous report[1], the possibility of using a long-acting nitrate compound for treatment in the acute phase of myocardial infarction was investigated. The result showing less total mortality, and less incidence of ventricular fibrillation without significant vasodepression, was encouraging. It was suggested that an improvement of cardiac function (viz: coronary artery vasodilatation, reduced cardiac work, and increased oxygen delivery to the myocardium) as shown in other laboratory studies, might indicate a logical extension of the use of nitrates to the period immediately following a coronary occlusion. In order to pursue this hypothesis further, and to extend the dosage of nitrate to the point of tolerance, we have undertaken the following work.

METHODS

All studies were carried out in mongrel dogs weighing between 24 and 38 pounds. The majority of the animals were young and appeared healthy. Anesthesia was given by intravenous pentobarbital and respiration was controlled with a Burns valve using automatic cycling and 100 per cent oxygen. Lead II of the electrocardiogram and constant blood pressure from the left femoral artery were monitored on a Sanborn multichannel amplifier. Twelve dogs were divided equally into control and isosorbide dinitrate treated groups. The experimental procedure consisted of: 1. Insertion of a left femoral cannula for recording blood pressure. 2. Left thoracotomy with dissection to expose the proximal portion of the circuflex coronary artery. 3. Administration of 20 mg. of isosorbide dinitrate in one to two minutes by intravenous infusion. (not done in control animals) 4. Rapid, one-stage ligation of the circumflex branch of the left coronary artery, 15 minutes later. The ligature was always placed within 0.5 cm. of the origin of the circumflex artery. 5. Closure of the chest wall was carried out within the next 30 minutes. No further therapy or supportive measures were given.

RESULTS

The results were analyzed by the following criteria: 1. Incidence of early mortality. 2. Incidence of ventricular fibrillation. 3. Effect on blood pressure. 4. Effect on electrocardiogram.

Table I presents the comparative incidence of early mortality and ventricular fibrillation in each group of dogs. The early occurrence of ventricular fibrilla-

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From the Department of Medicine and the Department of Surgery.
This research was supported by a grant from the Ives-Cameron Company, New York 17, N. Y., who also supplied the isosorbide dinitrate.

TABLE I

	No. of Dogs	Ventricular Fibrillation in 10 minutes or less	Survival of six hours or more
Control Dogs	6	4	2
Nitrate-treated Dogs	6	1	5

tion in the untreated group, ranging from 2 to 4 minutes post-ligation, was the most impressive difference. It appeared that the control dogs were susceptible to ventricular fibrillation while the nitrate treated dogs were protected. It should be pointed out that the rapid onset of ventricular fibrillation in the control animals necessitated the administration of a pre-ligation dose of isosorbide dinitrate to provide sufficient time to test the therapeutic effectiveness of the medication. The dogs were not monitored for longer than one hour after the coronary ligation was established, so the exact mode of subsequent death was not known. Since the duration of action of a single injection of isosorbide dinitrate is limited to approximately four hours, one would not expect a continued effect on the resultant animal mortality beyond this period.

The changes in blood pressure observed are of primary importance because of previous references[2,3] to the deleterious action of nitrates. A reduction of blood pressure averaging 18 mm. of Hg. was noted in response to the 20 mg. dose of isosorbide dinitrate given intravenously. This was approximately ten per cent of the systolic control blood pressures. The diastolic blood pressures maintained their same ratio to the systolic pressures in the control, nitrate-treatment, and post-ligation periods.

It should be *emphasized* that the dose of nitrate used was large, ranging from 1.2 to 1.8 mg. per kilo, in contrast to the suggested therapeutic I.V. dose of 0.1 mg. per kilo. These data are presented in Table II. The post-ligation blood pressures in the control and nitrate-treated dogs were no different when compared at the thirty minute interval. Thus, even though the treated dogs had a nitrate induced blood pressure deficit at the time of coronary occlusion, the resulting fall of systolic pressure was less in this group than in the controls. Figures 1 and 2 show a graphic representation of blood pressures recorded during the study of the two groups of dogs. The total depression of blood pressure, in response to coronary ligation, was about the same in the two groups and the ascending phase during recovery was not impaired in the nitrate-treated animals.

The electrocardiogram was not altered by the large dose of nitrate, except in one dog, in which the R wave amplitude was reduced to about one-fourth of its original height. This was the only dog in the treated group that encountered an episode of early ventricular fibrillation. The association of a nitrate induced electrocardiographic change, and an early post-ligation ventricular fibrillation in this dog, suggests that there is a limit to nitrate dosage which should not be exceeded. Since we used from ten to twenty times the recommended intravenous dose of isosorbide dinitrate, we feel that this will not constitute a difficult management problem in the future. In analyzing post-ligation electrocardiograms, there was a general im-

TABLE II

	No. of Dogs	Average Systolic B.P. Fall 15 min. after nitrate	Average Systolic BP Fall 30 min. after Ligation
Control Dogs	6		29.6 mm Hg.
Nitrate-treated Dogs	6	18 mm Hg.	29.0 mm Hg.

pression in this and other of our nitrate-treated series that evidence of acute-phase injury of the myocardium was not as extensive when isosorbide dinitrate was given. In the nitrate treated group there was lessened ST segment deviation and an earlier return to normal of ST segment and T wave changes.

In regard to post-ligation mortality (Table I), five of the treated group lived more than six hours while only two of the controls survived this length of time. The fact that an occasional laboratory animal can survive a nearly 100% fatal coronary artery obstruction, can be attributed to inherent differences in the distribution of the coronary artery collaterals, as demonstrated by Lumb and

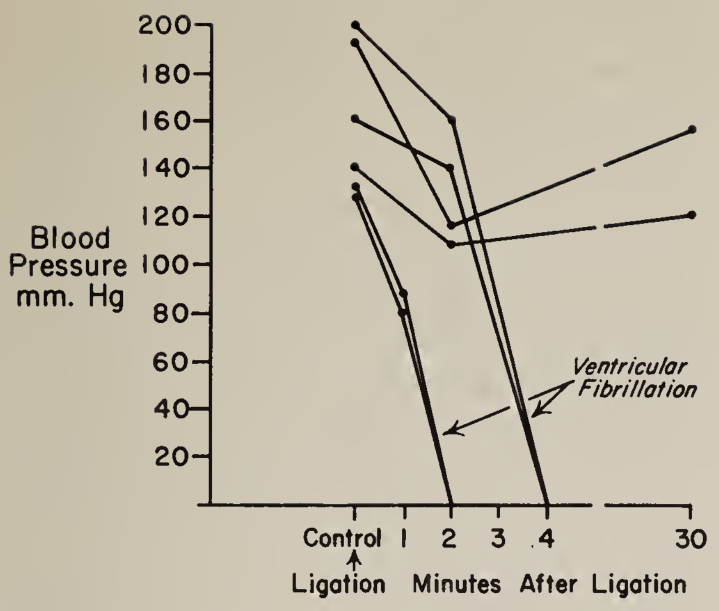

Fig. 1.—Acute ligation of proximal left circumflex artery with systolic blood pressure response—control dogs.

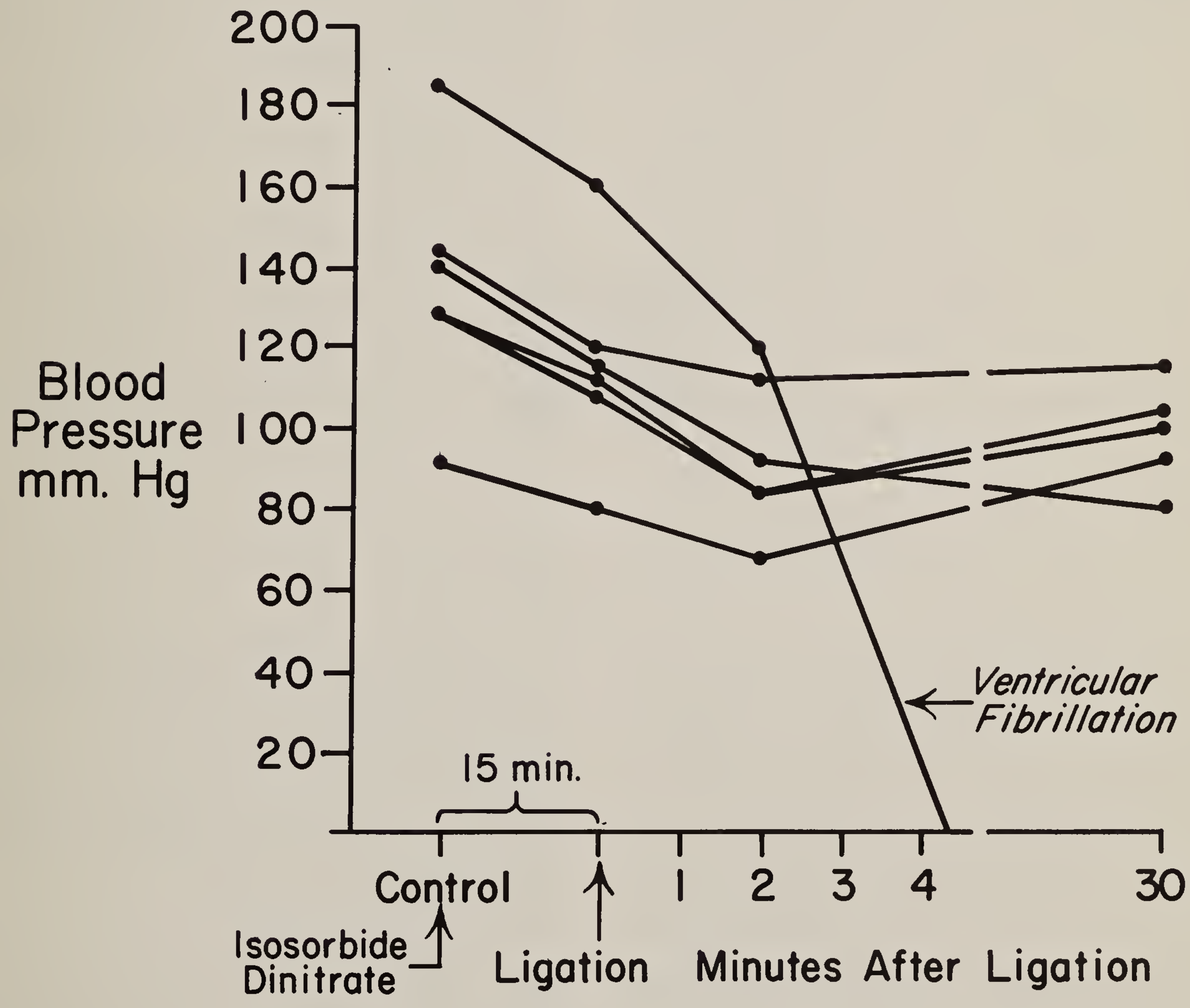

Fig. 2.—Acute ligation of proximal left circumflex artery with systolic blood pressure response—dogs pretreated with 20 mg. of isosorbide dinitrate.

his group[4]. They also found that coronary occlusion produced by Ameroid constriction was invariably associated with fatal ventricular fibrillation in a high percentage of control animals. Their nitrated-treated group showed a significantly increased survival rate, correlating well with our results.

DISCUSSION

It has been well established that nitrates produce active vasodilatation of the coronary arterial system. The resultant increase in coronary artery perfusion, especially in precapillary arterioles, is the important end point to be considered. It is in this aspect of coronary hemodynamics that nitrates are probably most effective. The small collateral blood vessels of the heart, of less than 40 micra in diameter, are present anatomically but exist as end arteries until the pressure dynamics of the coronary system promote their "development." The presence of this collateral system can be demonstrated by the injection of a thin medium into any coronary artery, with filling of the remainder of the coronary arterial system, even though a well functioning collateral circulation is not present. Jacoby and his group[5] have recently substantiated this in another way, showing rapid establishment of coronary collaterals by forced intra-arterial diastolic perfusion. This suggests that factors other than coronary artery obstruction and anemia influence the development of the collateral circulation.

In a therapeutic program designed to overcome obstruction to coronary blood flow, it is possible that nitrates may implement perfusion of the collateral circulation of the heart to produce a more evenly oxygenated myocardium. This would help to modify a sharply defined border of cyanotic and oxygenated myocardium with its propensity of cardiac irritability. It is possible that this defect is diminished in the nitrate-treated dogs, with reduction of the current of injury resulting in a lower incidence of ventricular fibrillation.

It has been experimentally demonstrated in dogs that a sudden ligation of a major coronary artery at its base produces a high percentage of early ventricular fibrillation. Harris[8] has eliminated this problem by first ligating the coronary artery over a 20 gauge needle and quickly removing it from the tie, followed by a complete ligature 30 minutes later. Lumb and his group[7] found that an acute ligation of the proximal portion of the left circumflex coronary artery produces the highest mortality of any single vessel ligation of the coronary system of dogs, with an early mortality of 83%. Friedberg[8] stresses the fact that acute experimental coronary occlusion differs from human cases, in that the latter are usually preceded by a prolonged period of progressive coronary obstruction, during which there is an opportunity for the development of some collateral circulation. It is evident that the coronary ligation produced in our studies constitutes one of the most severe tests of coronary artery impairment which can be carried out.

The dogs in this study received only a single intravenous injection of isosorbide dinitrate, given fifteen minutes prior to the coronary ligation. It would not be expected that one dose of this medication would affect the long-term mortality. However, definite reduction in the early mortality of the treated group was observed, due primarily to less ventricular fibrillation in the immediate post-occlusion period. This raises the possibility that nitrates may act prophylactically in the treatment of ventricular fibrillation in clinical coronary thrombosis. The search to find such an agent has been pursued vigorously in recent years. Only quinidine and procaine amide have been effective, each of these having toxic qualities.

The results of this work have shown that a large dose of intravenously administered nitrate does not produce an increase in mortality in experimentally produced coronary occlusion. This is in contrast to a considerable amount of current teaching. Even with the initial nitrate-induced fall in blood pressure, post-occlusion blood pressures were not different in the two groups. Evaluation of these facts leads to some optimism that the newer, long-acting nitrates may be potential therapeutic agents for human myocardial infarction. With the use of proper dosage, peripheral vasodepression should not be a significant problem. The patient with acute coronary thrombosis in shock requiring vasopressors for support, may be the ideal candidate for the use of combined therapy with nitrates. It is here that anti-fibrillation action is most needed because of the tendency for these drugs to produce serious arrhythmias. A well coordinated program of checks and balances in therapy should produce the optimum physiologic result. This will include, providing an augmented coronary arterial perfusion without peripheral vasodepression, increasing oxygen delivery to the myocardium at the cellular level, and neutralizing tendencies of ventricular fibrillation.

SUMMARY

With the exception of one dog, all animals of a nitrate-treated group lived a significant length of time after a coronary artery ligation which produced an increased incidence of fatal ventricular fibrillation in the controls. The dog heart does not appear to be overly sensitive to large doses of a long-acting nitrate, even in the face of some peripheral vasodepression. The ability of this drug to be therapeutically effective in cases of human coronary thrombosis should be the subject of future investigation.

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THE EFFECTS OF FOCAL FREEZING ON THE CENTRAL NERVOUS SYSTEM

Raymond A. Clasen, M.D.
Pauline M. Cooke, M.D.
Sylvia Pandolfi
George Carnecki, B.S.

INTRODUCTION

The use of focal freezing as a means of producing brain injury dates back to the nineteenth century. Its major use has been in the development of model experimental systems for the study of epilepsy, tissue necrosis, and edema under controlled conditions in the mammal. More recently the technique has found use in therapy of brain tumors and Parkinsonism in the human. The bibliography lists all the publications in English of which we are aware. It may be noted that more than two-thirds of the papers referred to have appeared within the last five years.

HISTORICAL REVIEW AND MORPHOLOGIC CHANGES

The literature on experimental freezing lesions of the brain dates back to 1883 when Openchowski first used the method in the study of the localization of cortical functions.* Freezing was induced by the application of a glass instrument cooled by ether vapor to the exposed brains of rabbits and dogs. In the latter, convulsive phenomenon were observed. Speransky extended this work in a large series of experiments in dogs beginning in 1926[41]. The lesions were produced by the application of a metal instrument cooled by carbon dioxide to the exposed dura. Speransky's principal interest was the study of the convulsive state. His monograph contains only a single gross photograph of a cerebral leson and a meager unillustrated histologic description.

The earliest paper of which we are aware in the American literature on the subject of cerebral freezing is that of Schneider and Epstein[38]. These authors attempted to reproduce in cats with ether anesthesia the experiments re-

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From the Division of Pathology

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*quoted by Speransky[41]

ported five years earlier in dogs by Speransky in the French literature. The latter author apparently did not mention the importance of morphine narcosis in the production of these convulsions in his earlier papers, although this is stressed in his monograph. Schneider and Epstein report the absence of convulsions and give what is apparently the first adequate description of changes produced in the brain by focal freezing. They exposed the brain and applied carbon dioxide snow or an ethyl chloride spray for one minute. On the first day after freezing, no histological changes were seen. One week later there was a slight degree of chromatolysis in the neurons of the outer cortical layers. At three weeks the marginal glia were increased. By three months the cortex was almost normal. In view of our observations and those of other authors, these results are rather surprising and indicate that focal freezing may produce a reversible cerebral lesion if the injury is mild. This is an important point which will be considered again in the section on therapy.

Cerebral lesions produced in rabbits by freezing with carbon dioxide through the intact skull were first described by Hass and Taylor[18,19]. In contrast to the lesions described above, these, and others to be mentioned, are the result of severe injury producing irreversible changes. Necrosis of cells, congestion, thrombi, hemorrhage and edema were noted a few hours after the lesion had been produced. In addition, edematous changes were seen adjacent to the areas of damage. Acute inflammation was mild and there was no suppuration or liquefaction necrosis. After the first few days macrophages appeared. By five weeks the lesions were small glial scars. Similar changes have been reported by Brierley[3] who also produced lesions in rabbits through the intact skull but used liquid air rather than carbon dioxide. According to Brierley, three hours after injury the damaged area is unstained in Nissl preparations and edmatous changes are observed in the white matter below the lesion. After one week gitter cells were noted in the base of the lesion. Mesodermal proliferation occurred in the next 2-3 weeks and there was a moderate increase in astrocytes in the boundary zone. From one month on, there was a progressive separation of the lesion by dense connective tissue.

The use of liquid nitrogen in the production of cerebral lesions was first described by this laboratory[5]. Lesions in the dog show changes similar to those described in the rabbit, except that the edema in the adjacent white matter, relatively inconspicuous in the rabbit, is one of the most marked features in these higher animals four hours after freezing. In addition, Rosomoff[33] has described polymorphonuclear infiltration after 4 hours with maximum intensity at 12 hours. Lesions in the dog have also been described by Ries and Tytus[32].

More recent studies in higher animals has included the work of Balthasar[1] and Klatzo et al[22] in cats. The latter experiments involved exposure of the brain and the application of a freezing instrument directly to the cerebral cortex for a period of 20 seconds. Immediately after freezing there was an increased vascularity in the frozen areas and both neurons and glia were pyknotic. At six hours these cells had disintegrated and there were edematous changes in the adjacent white matter accompanied by a marked enlargement of astrocytes. This was described as being maximal at 24 hours and subsiding at 48 hours. "Gitter cells" were described in the lesion at 7 days and the zones which were edematous showed hyperplastic astrocytes which were still present after 95 days[37]. Enzymatic changes were also described in these cells. Similar changes have been reported in the rabbit[30]. From one month on, the lesion was a glial scar.

One use of focal freezing has been the production of epileptogenic lesions in experimental animals. As was mentioned above, this was Speransky's principal interest and it was also the intent of Schneider and Epstein. Nims et al[29] used a method of freezing similar to Speransky to produce convulsions in dogs and one monkey with the additional help of morphine narcosis. Electroencephalographic changes were described in these animals and in cats. The latter animals did not receive morphine, however, and did not show clinical convulsions. Since deBarenne et al[2] had shown that local freezing of the cortex was associated with an alkaline change in the tissue while thermocoagulation was associated with an acid change, Marshall et al[26] attempted to relate this to the occurrence of convulsions and analyzed the brain chemically after focal freezing and thermocoagulation in the cat. Both methods of injury produced increased concentration of lactic acid and inorganic phosphates together with decreased concentrations of phosphocreatinine and hexose phosphates but these changes were greater with thermocoagulation than with freezing. More recent descriptions of the electrical discharge associated with focal freezing are in the papers of Keith and Bickford[20], Morrell and Florenz[28], Morrell[27], and Wada and Cornelius[43]. The latter authors combined freezing with intracortical injections of aluminum hydroxide and studied the electrical activity of deep structures as well as of the cortex. Clinical convulsions were reported by Morrell[27] "commonly" with lesions in rabbits near the motor cortex and by Wada and Cornelius[43] in the "majority" of cats with the combined lesions. In neither case was the use of morphine mentioned.

NECROSIS AND HEMORRHAGE

Another use of focal freezing has been in the study of effects of necrosis and hemorrhage on the brain. Of these, the most important acute effect is the development of edema in and around the lesion. We shall consider first the total effect of the lesion and in the section below attempt to separate those effects which may be specifically related to this secondary edema. For cortical lesions, the lethal effects are directly related to the size of the lesion. This has been shown for both the rabbit[19] and the dog[39]. Furthermore, the effect of multiple simultaneously placed lesions in the former animal is additive. Lesions placed at successive time intervals have shown that the lethal factor is active for about 48 hours after injury. Thus, lesions placed at a 48 hour interval are additive while lesions placed at a 72 hour interval act like separate lesions with respect to their effect on mortality[19].

Several attempts have been made to treat animals with these lesions in an effort to reduce mortality. Thus, it was shown that rabbits could be effectively treated by surgical decompression or pretreatment with hypothermia and prednisolone, but not with intravenous hypertonic glucose given after injury[31]. Prednisolone alone was not effective and hypothermia alone resulted only in an increase in survival time not in survival rate. The lesions used in this study resulted in the death of the entire control group (i.e. L.D. 100). By reducing the size of the lesion to an L.D. 50, Rosomoff et al[35] were able to demonstrate that hypothermia alone was an effective means of therapy if applied within 3 hours after injury. The effect of prednisolone alone on a smaller lesion is not known.

These lesions are associated with a sustained elevated intracranial pressure and in dogs with the development of papilledema[5]. Papilledema in the dog develops concomitantly with the development of increased intracranial pressure and disappears immediately when the pressure falls to normal levels. In this, the dog differs from the human. The elevated intracranial pressure in the dog was reduced at least temporarily by the use of intravenous hypertonic glucose and in the monkey by the use of intravenous hypertonic urea[13,6]. Hypertonic albumin was less effective and hypertonic dextran actually increased the elevated pressures.

Our studies of electroencephalographic changes in the dog after acute closed injury have not disclosed the development of seizure activity[8]. However, the animals were maintained under nembutal anesthesia and were followed for only about 5 hours after injury. The frozen tissue became electrically inactive and remained so. Elsewhere, there was a reduction in the amplitude of the waves and slow wave activity became more conspicuous. After the initial decline in electrical activity, the electrograms of both hemispheres returned toward normal. All this occurred within the first hour after injury. Following this initial electrical plateau, secondary deterioration began. The decline was not correlated with the time at which the intracanial pressure reached its peak or any subsequent interval and the changes in pressure and electrical activity did not run parallel. In monkeys when some of the damaged tissue lay within the middle third of the length of the motor strip nembutal bursts were abolished[14].

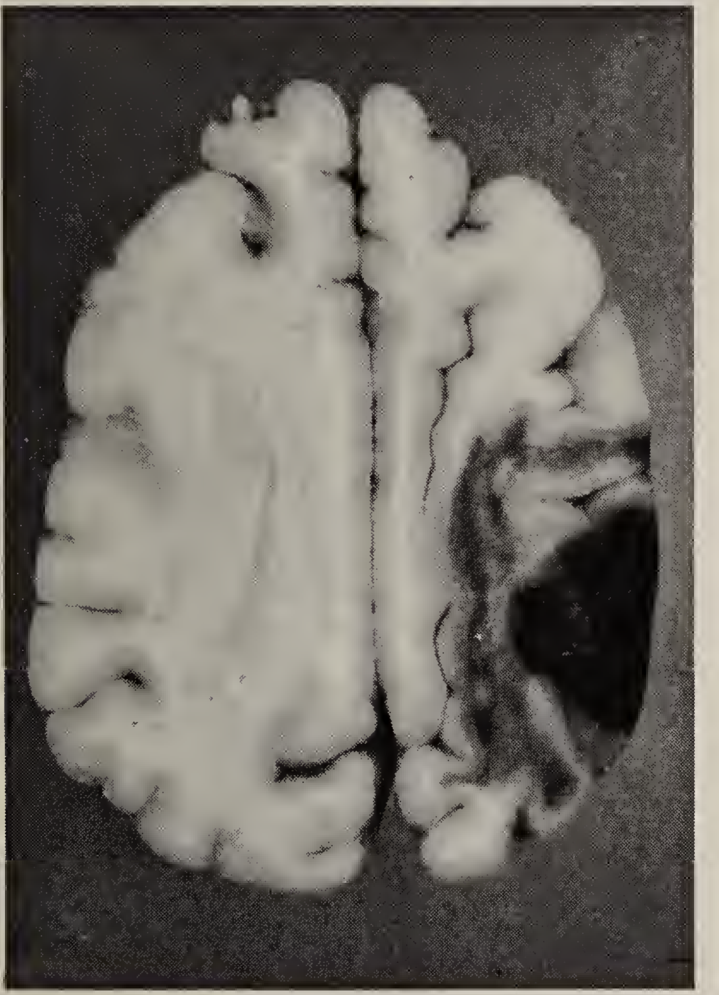

Fig. 1.—Cross section of dog brain four hours after damage. The animal had been given intravenous Evan's blue prior to injury. The lesion is intensely colored and well-circumscribed. Staining is also observed in the adjacent edematous white matter. Gray matter is not involved in this reaction to injury.

CEREBRAL EDEMA

Let us now consider which of these effects might be attributed to the secondary development of cerebral edema rather than to the primary effect of hemorrhage and necrosis. This edema is illustrated in Figure 1 taken from an animal given intravenous Evan's blue prior to production of the lesion. At one hour after injury the staining is restricted to the lesion. Four hours after injury the staining also involves the white matter adjacent to the lesion. Such areas show, on histologic examination, a decrease in fiber density indicative of a fluid increment in the hemisphere. (Figure 2) Characteristic sparing of the gray matter and arcuate fibers may be noted in this reaction to injury.

First of all, we may ask if the lethal factor described above is, in part, the progressive cerebral edema which accompanies these lesions. Rosomoff[33] has shown that in the first hour after injury in dogs there is an increase in the mass of the damaged hemisphere. This is followed by a slower progressive increase in size up to 12 hours after injury. The mean survival time in dogs with lethal lesions is 8.3 hours. There is some evidence that the maximum edema associated with these lesions may occur about 12 hours after injury[9]. While damaged cells may release toxic substances into the surrounding tissues, the fact that rabbits were benefited by simple decompression indicates that if this factor played a role in the death of the animals, it was a secondary one. Hemorrhage is also a space-consuming lesion which is important in large lesions that lead to death in a few hours[31] but quantitative data in the dog and monkey have shown that it is not progressive. Cerebral edema may therefore be viewed as an important part of the lethal factor associated with these lesions.

With these facts in mind, we may ask if the effective means of therapy which have been described diminish this edema. Clearly, the space-consuming effects of the edema and hemorrhage are reduced by surgical decompression. Rosomoff[33] has shown that although the hypothermic animal does develop a mass increment one hour after injury, which may be attributed directly to the lesion, they fail to develop the progressive increment even after 36 hours. These results were essentially confirmed in cats by Laskowski et al[23] who evaluated the edema by qualitative histological means and vital staining. We may thus attribute the beneficial effects of hypothermia to a suppression of the progressive edema which accompanies these lesions. The exact mechanisms by which this occurs is not known but it is of interest to emphasize Rosomoff's finding[35] that it was necessary to maintain the hypothermia for only one hour to demonstrate a protective effect. These animals failed to develop edema even though they attained normal body temperatures.

The mechanism by which the combination of hypothermia and prednisolone decreased the mortality in rabbits with these lesions is obscure. The beneficial effect of prednisolone in this case cannot be ascribed to a depression of cerebral edema since we have no evidence that there was a progressive space-consuming lesion in hypothermic rabbits and the data of Rosomoff in dogs suggests that there was not. Whatever the mechanisms by which this combination decreased mortality, the fact remains that it did so. Our experimental results indicate that in those clinical conditions involving cerebral injury in which hypothermia is found to be effective[34], the addition of prednisolone to the hypothermal regimen should increase its effectiveness.

We might suppose that the increased intracranial pressure associated with these lesions is a reflection of the accompanying edema and that changes in this pressure would reflect changes in this edema. A careful analysis of experimental data shows that this is not the case. First of all, the time course of the pressure changes is not the same as the edema. The pressure increases from 100 mm. to about 300 mm. within 30 minutes after injury while the edema takes several hours to develop[5]. Furthermore, there is not a progressive rise in intracranial pressure in the next 12 hours[35]. Secondly, although lesions made in hypothermic dogs are not associated with progressive cerebral edema, they are associated with elevated intracranial pressure of a magnitude equal to that seen in the normothermic group[35]. Although animals with delayed hypothermia following a freezing lesion show a decrease in intracranial pressure while their body temperatures are reduced, this pressure promptly returns to its previous level when these animals are rewarmed in spite of the fact that such animals show the protective effects of hypothermia on mortality. Thus, the absence of progressive cerebral edema with these lesions is not associated with a decrease in the elevated intracranial pressure. Thirdly, although the intravenous administration of both hypertonic glucose[13] and urea[6] results in a decrease in the elevated intracranial pressure associated with these lesions, this is not accompanied by a decrease in the water increment of the damaged hemisphere. We have recently shown that this decrease in the case of urea is due to abstraction of water from the undamaged hemisphere of the monkey.* This occurs without a concomitant decrease in tissue

Fig. 2.—Microscopic preparation of monkey brain four hours after injury. Normal gray matter to the left; normal white matter at the extreme right. The edematous area shows a decrease in nerve fiber density indicative of a fluid increment at this site. Luxol fast blue hematoxylin stain.

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*Unpublished data

chloride. Thus, a measured decrease in elevated intracranial pressure is not associated with a decrease in cerebral edema. From these facts, one can conclude that the elevated intracranial pressure associated with these lesions is a direct reflection of the lesion itself, i.e. hemorrhage and necrosis and not a reflection of the progressive cerebral edema which accompanies the lesion.

With respect to the electroencephalographic changes, the electrical inactivity of the damaged area is due to hemorrhage and necrosis. The primary decline in electrical activity is probably also a direct effect of the lesion. However, the secondary decline, after what amounts to an electrical lucid interval, is presumably a physiologic reflection of the developing edema. It remains to be shown whether these changes can be prevented or reversed by therapeutic measures which reduce the edema.

Our interest in freezing lesions was and is for elucidation of therapeutic mechanisms. Hence, we have produced large lesions for maximum lethal effect. The primary interest of Klatzo and his associates has been the histology of the edema accompanying the lesions. Hence, these authors have produced small cortical lesions to minimize the other effects of hemorrhage and necrosis. The histologic characterization of this type of edema given by Klatzo et al[21,22] is the most extensive published to date. It is of interest that one month after injury the nerve fibers in the white matter under the lesion appeared normal. We have made similar observations in the dog. Morrell, on the other hand, has reported a loss of myelinated fibers in the white matter adjacent to the lesion in the rabbit three months after injury[27]. He did not, however, study this question critically and from his only published illustration it is not clear that this white matter was not included in the primary lesion. It is probable that the axons from neurons included in the lesion degenerate and disappear. However, in the case of the higher animals there are so many more nerve fibers in the centrum ovale and gyral cores that this difference is not apparent with ordinary staining methods for axons and myelin.

To date, only two groups of workers have used freezing lesions to study the electron microscopy of cerebral edema. In the first of these by Torack et al[42] rats and mice were used. Histologic evidences of edema were described in the corpus callosum and the reaction was said to be maximal at 48 hours. Electron microscopy revealed an enlargement of the cytoplasmic volume of clear glial cells and the authors concluded that this type of edema was an intracellular process. Luse[24] on the other hand studied the process in the white matter of cats 6-24 hours after freezing. In a brief abstract she describes only swelling of the perivascular space. Since by light microscopy the process clearly extends beyond this point and since Torack et al[42] offered no quantitative evidence that edema was actually present, at the times when the brains were studied, it is our opinion that further electron microscopic study of this type of edema is indicated.

The correlation between histologically recognizable edema, vital staining with Evan's blue and positive staining with the periodic acid Schiff (PAS) technique (Figure 3) was described several years ago[7]. It is important to emphasize that the dye must be given prior to production of the lesion in order to observe an exact temporal and spatial correlation with developing edema. Thus Klatzo[22] did not observe an exact correlation between histologically-recognizable edema and fluorescence when the fluorescein was given after production of the lesion. Wright and Soloway[44] did not observe a special correlation between trypan blue staining and the uptake of m-boronosuccinailic acid when these substances were given 2 hours after injury. Since we have recently shown that vital staining in the first 12 hours after injury is a reflection of the exudation of serum albumin[4] which is normally present in the mammalian extracellular space, it is tempting to correlate the PAS staining with the presence of such a space in edematous white matter. Perhaps there are two forms of edema in the central nervous system, an extracellular form which is PAS positive and an intracellular form which is PAS negative. This should be thoroughly investigated in human material. Our own observations indicate that either type may occur in the presence of inflammatory and neoplastic conditions.

From a study of the edematous zones in the dog it became apparent to us that the development of the edema around these lesions was related in some way to the fiber systems of the white matter. Since this aspect of the anatomy of the monkey brain had been described in great detail by W. J. S. Krieg, a series of experiments were conducted in this

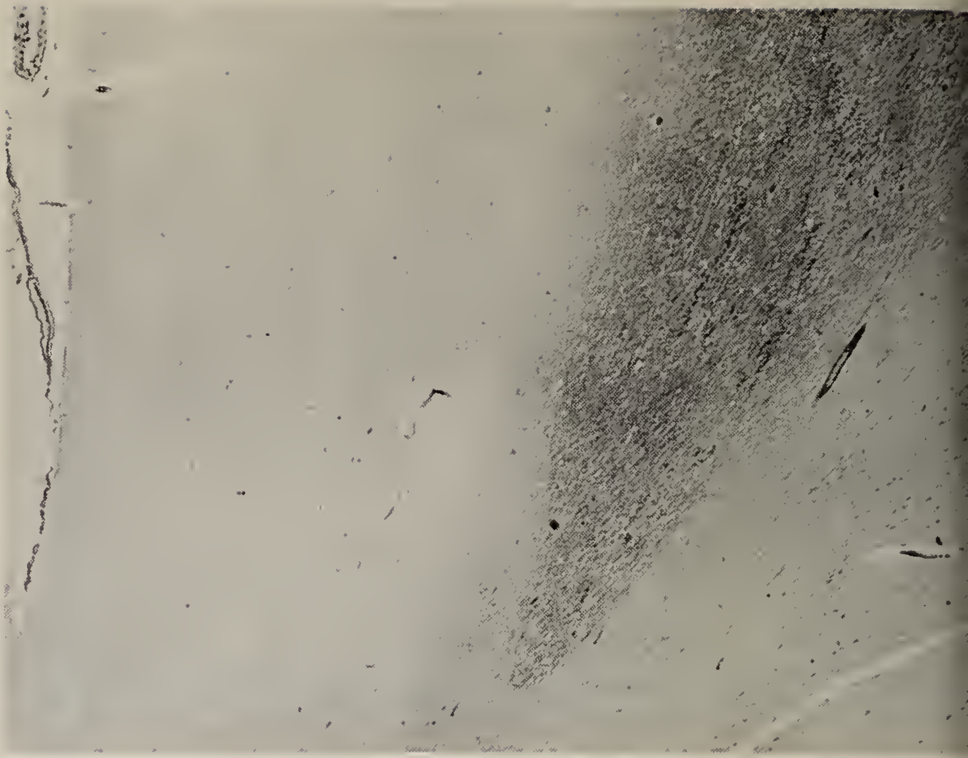

Fig. 3.—Same as Figure 2. Periodic acid-Schiff stain. The edematous area stains positively.

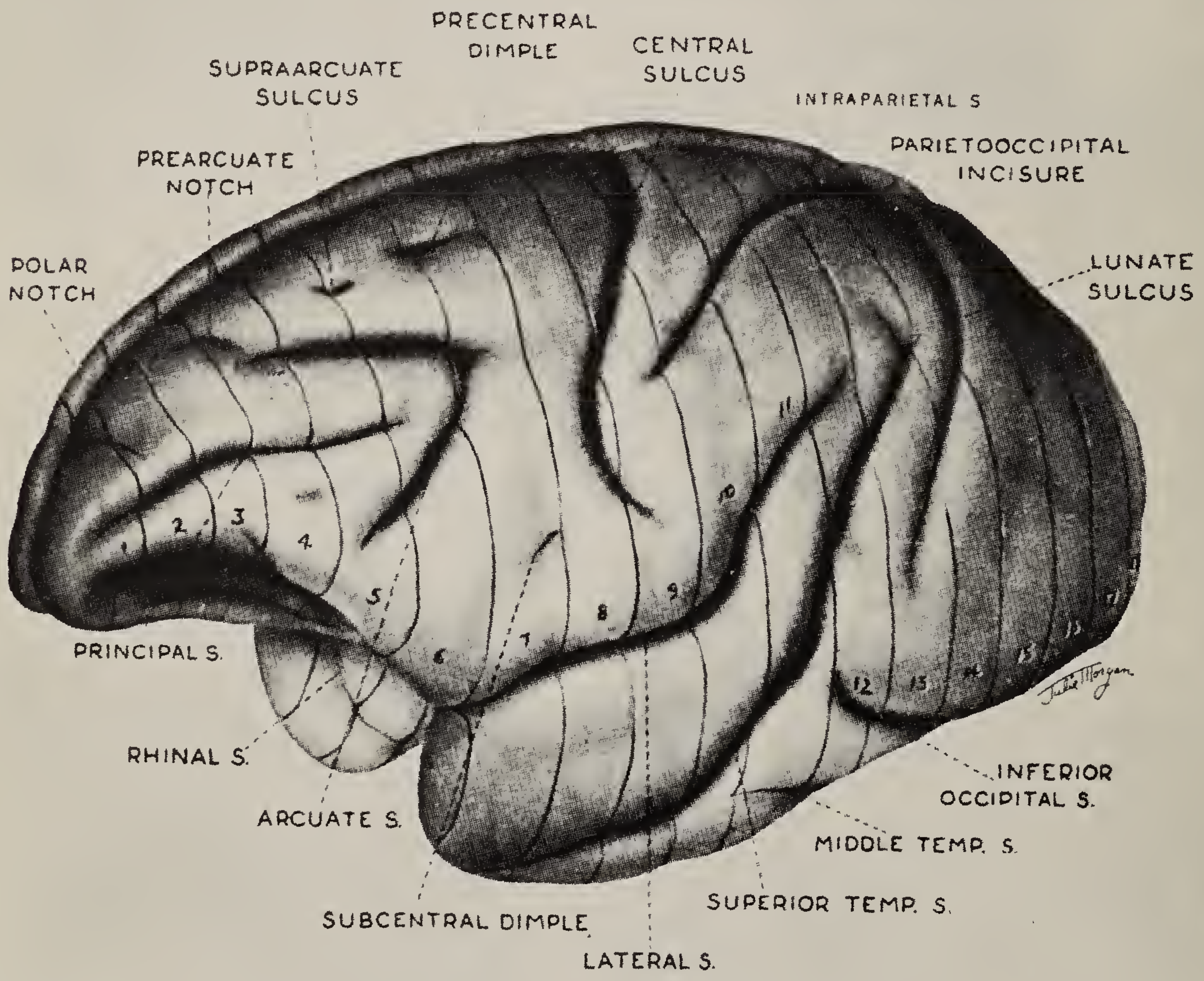

Fig. 4.—Macaque brain showing standard slices. From "Connections of the Frontal Cortex of the Monkey" by Wendell J. S. Krieg, Published by Charles C. Thomas.

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animal[10]. In his anatomic studies, Krieg first developed the concept of a standard monkey brain divided into a series of slices (Figure 4). Small cortical lesions were made in the brains of a large series of monkeys. After the appropriate time interval, the animals were sacrificed and the brains studied by the Marchi method which demonstrates degenerating fiber tracts. Data from serial sections were then transferred to drawings of the standard slices (Figures 5 and 6) so the results from many lesions could be compared with one another. In this way, the fiber anatomy of the frontal lobe and the post central gyrus was described. Data on the remainder of the cerebral hemispheres will be published in the near future.

In our own experiments the presence of cerebral edema was evaluated by observing the degree of vital staining with Evan's blue, making use of the empirical observation described above. The extent of the lesion, as well as the peripheral staining of white matter, was recorded on photographic reproductions of Krieg's standard slices. In doing this, a certain amount of interpretation was necessary since individual monkey brains are often not standard. These difficulties may be appreciated by comparing Figures 5 and 6 with photographs of the actual specimens published in our recent paper[10]. The advantages gained from being able to compare the entire series with one another, however, greatly outweighs these difficulties, and having our data recorded on the standard slices enabled us to directly compare the peripheral staining reaction with the Marchi patterns described by Krieg.

In studying this material, no correlation was observed between these parameters. The peripheral staining reaction was always less than would be anticipated from the Marchi patterns. There was, however, a definite difference in susceptibility to the development of edema between the gyral core of the pre and post-central gyri. This was a consistent

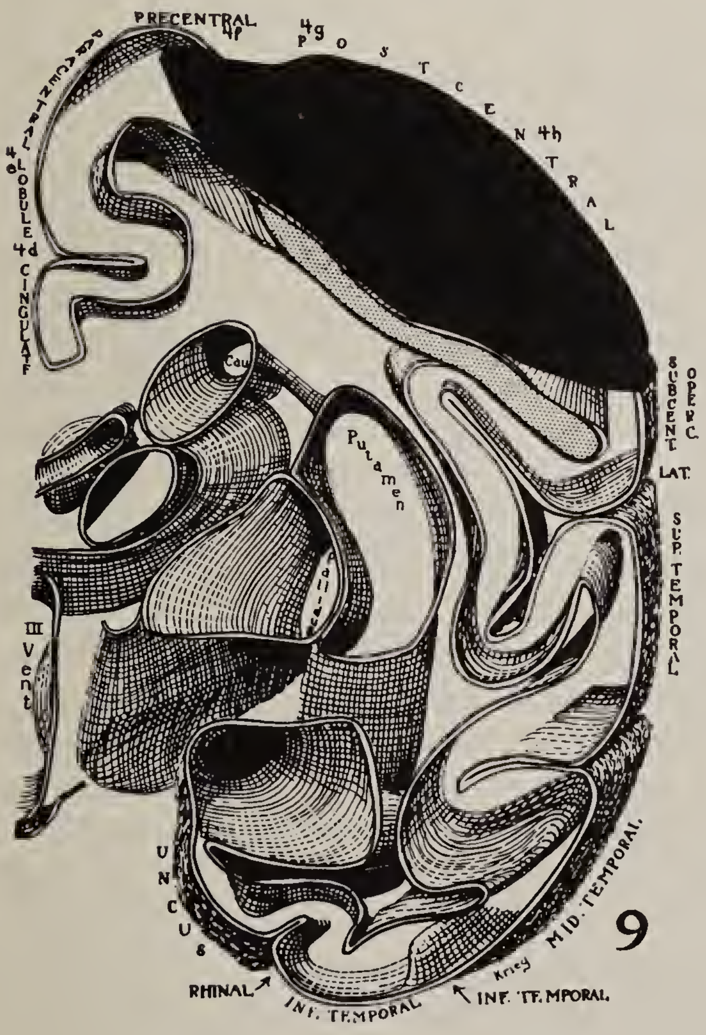

Fig. 5.—Lesion and edema from experiment 53, reproduced on standard slice #9. From an original drawing by W. J. S. Krieg. Black-lesion. Dotted areas—edema.

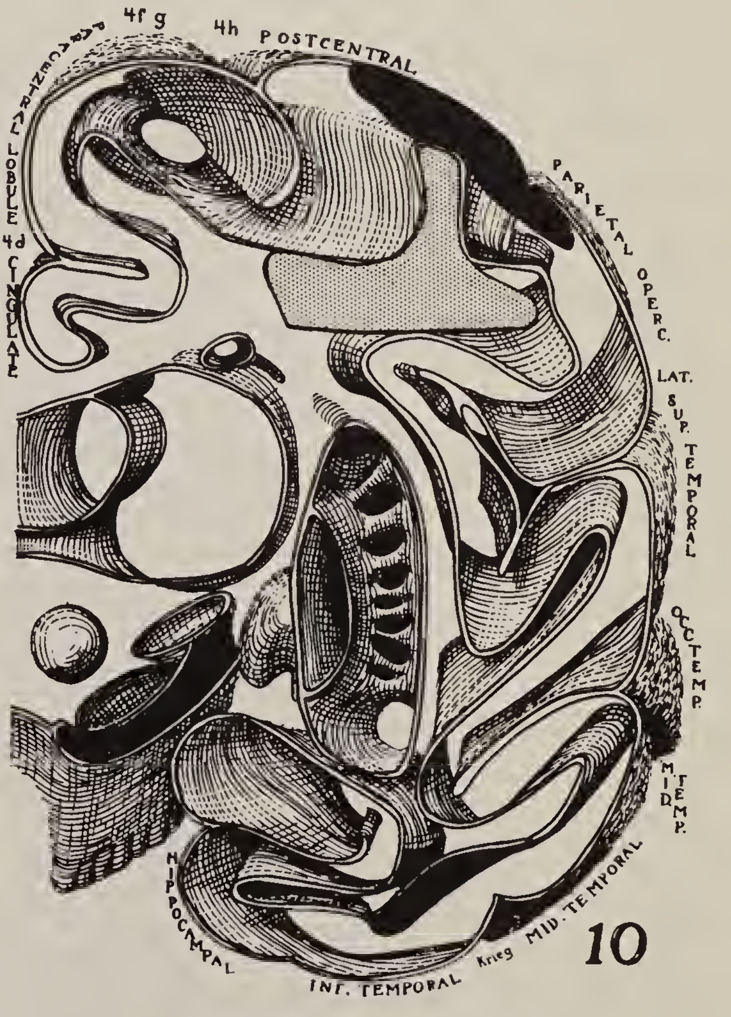

Fig. 6.—Lesion and edema from experiment 53, reproduced on standard slice #10. From an original drawing by W. J. S. Krieg. Black-lesion. Dotted areas—edema.

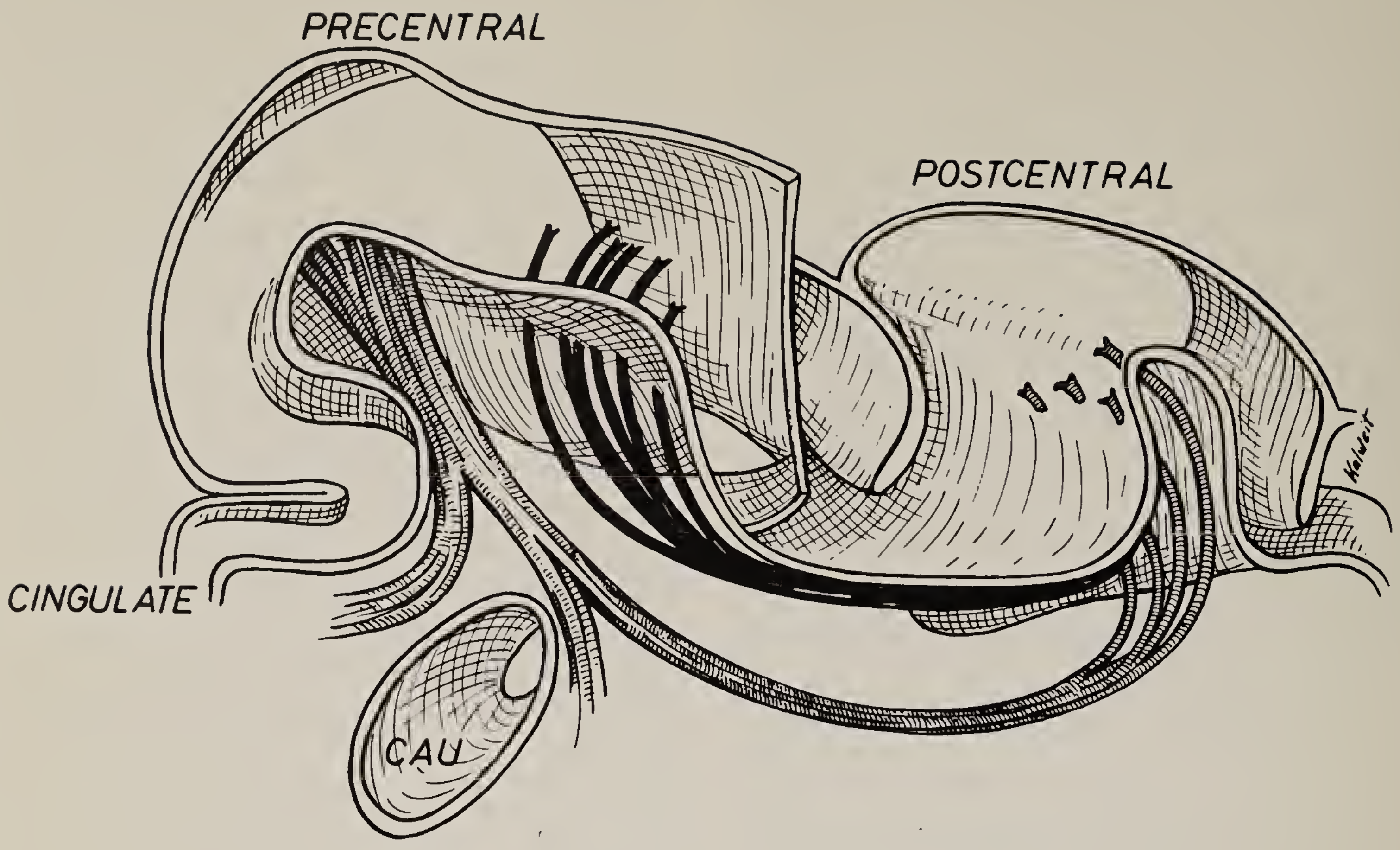

Fig. 7.—Diagramatic representation of the fiber pattern of the pre and post-central gyri based on the descriptions of W. J. S. Krieg. Cross hatched—fibers from area 4 (FA). Black-associational fibers from area 1 (PC).

finding for the entire series and is illustrated in Figures 5 and 6, taken from one of our experiments. Definite staining was noted in the post-central gyrus, while the precentral gyrus was spared in spite of the fact that it lay adjacent to a rather massive lesion. The reason for this is to be found, we believe, in the fiber anatomy of these areas, as described by Krieg. This is summarized in Figure 7 which is a composite drawing of the supero-medial aspect of standard slice number 9 and the supero-lateral aspect of standard slice number 10. The precentral gyral core contains projectional fibers from area 4 (FA) which are coarse. They are represented by cross-hatching in the drawing. Callosal fibers are continuations of the projectional fibers and cortico-thalamic fibers veer from the projectional fibers in the internal capsule. The bulk of the arcuate fibers underlying the central sulcus represents associational fibers from area 1 (PC), located in the post-central gyrus, to the posterior bank of the precentral gyrus, area 4 (FA). These are shown in black. Associational fibers from area 4 (FA) in the precentral gyrus to area 3 (PB) in the post-central gyrus must, therefore, course around these arcuate fibers to enter the anterior band of the post central gyrus. The net result of all this is a fiber pattern in the precentral gyrus which is relatively parallel and close, and in the post central gyrus, one which is criss-crossed and more widely spaced. There is thus a parallelism between fiber pattern and susceptibility to edema, the closer the fibers, the less the susceptibility. This also explains the relative sparing of arcuate fibers and the relative sparing of the corpus callosum, long known to be a property of cerebral edema in man.

The electrolyte chemistry of cerebral edema has also been studied using this model system. The analysis of data has been difficult. Although we have published preliminary reports[11,12] we hesitate to say much more than that the electrolyte changes in the damaged hemisphere are very complex and cannot be reduced to a simple increment of blood and serum in the damaged hemisphere. The earliest chemical change associated with the appearance of edma is a disproportionate increase in tissue sodium. The maximum electrolyte changes, however, appear to occur around 12 hours after injury.

THERAPEUTIC APPLICATIONS

Finally, the more recent direct application of the freezing technique in the treatment of human diseases may be mentioned. Rowbotham et al[36] have explored the possibility of using the technique for destroying deep-seated brain tumors. It was used in three cases and shown to be at least safe. The other direct application of the technique is that of Cooper[15,17] who is using it in basal ganglia surgery for treatment of Parkinsonism. Reversible histologic lesions were described in the original paper of Schneider and Epstein[38]. Mark et al[25] have demonstrated physiologically reversible lesions in the cat. A cooling probe was steriotatically placed near the third nerve nucleus. Lowering the temperature to 5° resulted in dilatation of the ipsilateral pupil. When the probe was removed the pupil contracted. These experiments were subsequently expanded to include a description of changes in evoked potentials in various areas of the cat brain following in situ freezing as well as the freezing of distant structures[40]. In Cooper's work the probe is used to test the physiologic effect of the lesion in the patient. If this proves satisfactory, an irreversible lesion is produced by lowering the temperature still further.

It is apparent from the above review that a good deal of work has been done in this area by many laboratories. It is to be hoped that the information gained in this way will prove of value to the clinician both in the treatment of the various forms of cerebral injury and in the use of the freezing technique for therapy.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Cardiovascular Surgery, by Ormand C. Julian, William S. Dye, Hushang Javid and James A. Hunter. *Year Book Medical Publishers, Inc., Chicago, 1962. pp. 335, 103 illustrations.*

This is the eighth Handbook of Operative Surgery published by the Year Book Medical Publishers. Its size, weight, pleasing appearance and strikingly effective and instructive semidiagrammatic drawings are up to the standards and often surpass those of the previous monographs.

The subject material is handled in three sections. The first section deals with the arterial system. After a brief clinical evaluation, operations for arterial injuries, acute arterial occlusions, chronic arterial occlusions, brachiocephalic arterial disease, hypertension due to renal vascular disease and arterial aneurysms are depicted. In the second section, varicose veins, stasis disease and the superior vena cava syndrome are dealt with. In the third section, after a succinct statement on general surgical techniques, surgery of the great vessels, pericardiectomy, mitral valve surgery, aortic valve surgery, pulmonary valve surgery, interarterial septal defects, interventricular septal defects, tetralogy of Fallot, transposition of great vessels and cardiac resuscitation are taken up.

This, then, is a truly ambitious undertaking. There is no description of sympathectomy, in spite of its great importance in the management of both peripheral and visceral arterial disease. Surgery for coronary and mesenteric circulation is not discussed. The subject of portal hypertension is not included. This self-imposed restraint of the authors is probably wise. It shows the ever expanding leld within the limits of specialization. The scope of cardiovascular surgery has widened so rapidly in the last two decades that a short, authoritative survey of established technical procedures is most welcome. This comes from a team of aggressive and experienced cardiovascular surgeons, and it may signify the termination of a first phase in the development of this specialty. This phase consisted of testing the limits of operability. While detailed indications and late results are purposely omitted, a healthy air of conservatism permeates the text.

The proofreading has been particularly meticulous. Only a few errors are apparent, such as in the spelling of Kouwenhoven, "communicative" veins and "quadrilateral" vein ligation. Being an operative manual, the reviewer missed a brief discussion of needles, suture material and prosthetic material. The authors have been pioneer contributors to this field and their choice of these ancillary measures would have been very instructive.

The institutions from which this monograph emanated, can be justly proud of this accomplishment. It should be particularly useful for the general physician, the internist and the general surgeon, whose contact with this specialized field is only occasional. With increased standardization of indications and techniques, it is probable that many of these procedures will pass over into the domain of general surgery—*(Geza de Takats, M.D.)*

Congenital Anomalies of the Tracheobronchial Tree and of the Esophagus. P. H. Holinger, K. C. Johnston, J. A. Schild. *The Pediatric Clinics of North America, Vol. 9, No. 4, November, 1962.*

Diagnostic and therapeutic problems of congenital anomalies of the air and food passages are reviewed. The various anomalies are described individually, with particular attention paid to the importance of cinefluoroscopy and the endoscopic aspects of diagnosis. Dramatic emergencies of respiratory or swallowing obstruction in infants may be due to these anomalies. The importance of the cardiovascular anomalies in regard to tracheobronchial and esophageal obstruction has been realized only relatively recently.

All diagnostic measures should be used to determine their presence or absence in infants with airway and esophageal obstruction. If doubt still remains after careful study, exploratory surgery may be lifesaving as the obstructing ring is severed.

The Growth of Transplanted Foetal Bones in Different Immunological Environments. J. Chalmers and R. D. Ray. *Jour. of Bone and Joint Surgery, February, 1962.*

1. Homografts of eighteen-day-old foetal femora in pure strains of mice showed no fundamental difference in behavior from grafts of more mature bone and cartilage.
2. Growth of bone was limited to a short period after transplantation and was abolished by previous immunization. Cartilage growth alone was responsible for the increase in size of these transplants and did not appear to be influenced by the presence of immunity.
3. There is no reason to suppose that bone from an immature source is likely to behave more favourably than more mature bone homografts in clinical use.
4. The limited growth of cartilage and the total failure of bone survival in the heterografts indicate an immune reaction of a different order from that which develops against the homograft.
5. The different effect of the homograft immune reaction on cartilage and bone enabled certain conclusions to be drawn concerning the part played by these two tissues in determining the form of a bone. Cartilage growth and development is shown to be regulated in large part by intrinsic factors. Bone growth and form on the other hand is shown to be dependent largely upon extrinsic influences.

Chemotherapy of Cancer of the Alimentary Tract. S. Economou and W. Cole. *Surgical Clin. N. Amer. Oct., 1962.*

Although there has been no dramatic breakthrough in chemotherapy of alimentary tract cancer there have been a sufficient number of modest advances to justify optimism. The authors emphasized the variety of methods, drugs and dosage schedules available and the importance of correctly applying these modalities to a particular clinical problem. Probably the most effective drugs in the palliative therapy of intestinal cancer are 5-fluoro-uracil and 5-fluoro-deoxyuridine. The methods of administration, dosage schedules and complications are discussed. One of the more prominent advances has been the reduction of suture line recurrence of intestinal cancer from an incidence 10% to the zero point. This was accomplished by the simple practice of colon division and re-anastomosis outside of lumen ties placed proximal and distal to the malignancy. Also, prior to the anastomosis the bowel lumens are rinsed with locally effective anti-cancer agents.

Experimental Production of Renal Hypertension. G. de Takats, B. L. Lindstrom, L. S. Medgyesy, L. Wibin. *Am. Surgery, 156:2, p. 292, Aug., 1962.*

Experimental renal hypertension can be readily produced by temporary or prolonged constriction of the renal pedicle, or by renal encapsulation. This type of renal ischemia, however, does not resemble primary (essential) hypertension.

The overwhelming majority of human hypertensives exhibit diffuse hyperplastic arteriolar sclerosis with thickening of the basement membrane of the glomerulus. In a group of 58 dogs, followed over a period from six months to two years, an attempt was made to produce sustained hypertension by injecting a sclerosing substance into one renal artery and removing the opposite kidney. It was possible to produce chronic hypertension when, 1) 1.0 percent Sotradecol was injected with simultaneous venous compression for one minute and; 2) a preliminary procaine injection was made either into the renal artery or into the renal pedicle. The dogs became vasolabile and their kidneys were more susceptible to hematogenous infection. The height of the blood pressure could be correlated with graded histologic damage. The juxtaglomerular cell counts, however, did not show sufficient difference at different levels of blood pressure.

Thus, a model has been produced, which closely resembles the clinical picture and the histologic findings of early, primary hypertension.

Studies of Papilloma of The Larynx. P. H. Holinger, K. C. Johnston, G. H. Conner, B. R. Conner and J. Holper. *Ann. of Otol., Rhinol. and Laryngol., Vol. 71, No. 2, June, 1962.*

Laryngeal papillomatosis in children or adults is a serious, debilitating problem. Failure to differentiate between true papilloma and laryngeal keratosis is responsible for confusion in the literature concerning the course of laryngeal papillomatosis. In previous reports the authors indicated the ease and rapidity with which tissue cultures of laryngeal papilloma appear to grow; apparently it is greater than cultures of embryonic or other adult tissues, benign or malignant. The influence of endocrine factors on laryngeal papilloma growth is noted in the clinical material presented, by the effect of puberty, pregnancy and direct topical application of hormonal agents. The most significant portion of this paper concerns viral studies with human laryngeal papilloma tissues. These have indicated the presence of a species-specific virus capable of producing growth of tissue cultures with regrowth on as many as eight passages. Serologic studies suggest that the cytopathogenic agent in the tissue cultures is a human virus capable of producing compliment-fixing antibodies. Animal inoculations of papilloma suspensions, egg cultures and tissue cultures of laryngeal papillomata were all negative, indicating an absence of other viruses and that the papilloma growth agent is species specific. Autogenous vaccines were prepared for and administered to eight patients with laryngeal papillomatosis; four adults and four children. The series is still too small to draw definite conclusions, but some encouraging results have been obtained.

Experimental Study of the Behavior of Adult Human Skin Homografts During Pregnancy. R. H. Andresen and C. W. Monroe. *Amer. Journal Obstet. and Gynec., 84:1096-1103, 1962.*

Full-thickness adult skin homografts were exchanged between human pregnant and nonpregnant hosts. First set adult human skin homografts survived for longer periods of time (18 days) on pregnant hosts, than on nonpregnant hosts. The human pregnant host, although subjected to a graft during a previous pregnancy, was capable of eliciting the second set rejection phenomenon. In this study, "tissue immunity" induced by transplantation of full thickness adult human skin homografts was operative in pregnant as well as in nonpregnant hosts for as long as 2½ years following initial grafting procedures. These experiments have provided a method of further inquiry into the tissue immunology of human pregnancy.

The Directed Isolation of Mutants Producing Increased Amounts of Metabolites. G. Scherr and M. E. Rafelson, Jr. *Journal of Applied Bacteriology. 25(2), 187-194 (1962).*

A method has been developed by which a culture of an organism is subjected to a gradient concentration of an antimetabolite whose increased yield is desired. Mutants that can survive the inhibitory concentration of the antimetabolite are picked as clones and show an increased yield of the specific metabolite over that of the parent from which they were derived. Two to eight-fold increments in yields of nicotinic acid, pyridoxine and thiamine were obtained in a single step isolation of such mutants. The details, significance and additional applications of the methodology are discussed.

Uteroplacental Trauma as a Method of Conditioning the Maternal Host to Adult Homografts. C. W. Monroe, R. H. Andresen, G. M. Hass, D. A. Madden and S. Swartzbaugh. *Ann. N. Y. Academy of Sciences, 99:733-742, 1962.*

The uteroplacental sites of rabbits at midgestation were traumatized by physical means capable of inducing the entry of cells from the uteroplacental sites into the maternal circulation. Following the trauma each pregnant host received a musculofascial transplant from a random adult donor. Two weeks later, the graft sites were prepared for microscopic analysis. This showed accelerated graft injury by the pretreated maternal host in 25 per cent of the homografts. These studies indicate that it is possible by the production of uteroplacental trauma prior to grafting to alter the local reaction of the pregnant host to homografts of adult tissues. Since uteroplacental trauma, per se, results, on occasion, in the enhanced production of conditioning mechanisms directed against homografts, it is possible that a tissue antagonism between maternal host and fetus may, at times, be perpetrated by the occurrence of natural disturbances at the uteroplacental site.

The Influence of an Increased Intraluminal Pressure on Intestinal Absorption. R. E. ANDERSON, W. E. SCHMIDTKE and W. G. DIFFENBAUGH. *Ann. of Surgery 156; 276-286; Aug. 1962.*

There is a great lack of information relative to the effect of an increase in the intraluminal pressure on the absorbing capacity of the intestinal mucosa. In an attempt to gain some fundamental knowledge on what this effect might be, a group of dogs was subjected to an experiment in which an isolated loop of either colon or small intestine was distended for periods of time ranging from 5 to 24 hours at pressures from 25 to 70 cms. of water. Measurement in the absorption was undertaken by the utilization of radioactive iodine which was placed into the loop and ultimately recovered in the peripheral blood. The percentages of absorption were then charted according to the type of pressure and time of measurement. Concurrent absorption and "rebound" absorption were studied.

Generally speaking, the results of the entire series of experiments indicate that absorption of radioactive iodine from the colon increases with a pressure elevation up to 50 or 75 cms of water. Beyond this, the pressure results in a decrease in intestinal blood supply and the absorption, in turn, decreases. This phenomenon is also observed in the small intestine. The elements of time and pressure appear to be about equally important to the overall increase in the absorption before gross evidence of loss in viability takes place.

Attempts to Influence Placental Aging by Activation of Mechanisms of Tissue Immunity. R. H. ANDRESEN, C. W. MONROE, G. M. HASS, D. A. MADDEN and S. SWARTZBAUGH. *J. Lab. and Clin. Med., 60:855, November 1962.*

Pregnant and nonpregnant rabbits show enhancement of mechanisms injurious to homografts of adult musculofascial tissues within 2 weeks following treatment with blood from multiple donors other than donors of grafts. Similar mechanisms directed against adult homografts in nonpregnant hosts can be mobilized by injections of pooled embryonic or placental tissues (2 weeks of age), prior to grafting from random donors. The following experiments were designed to determine whether or not it was possible to quicken the normal mechanisms of degeneration of uteroplacental tissues by challenging the maternal host at midgestation with fresh blood from multiple male donors. In individual experiments, the litter size of the maternal host (14 to 15 days of gestation) was determined by direct observation. To avoid hypervolemia, 20 ml. of maternal blood was withdrawn via cardiac puncture and discarded. Each maternal host then received 2.5 ml. of blood from each of 10 unrelated male donors. Two weeks later the maternal hosts were sacrificed and the number of living fetuses noted. The fetuses were removed and examined for splenic hypertrophy. The uteri were fixed and sections of the uteroplacental sites were prepared for microscopic study. All fetuses were normal with no gross evidence of runting syndrome. Microscopic analysis of the uteroplacental sites showed no unusual cellular changes. Under present conditions, it was not possible to disturb prematurely the natural mechanisms of deterioration of uteroplacental tissues by alerting mechanisms which accelerate injury to homografts of adult tissues.

Tracheogenic Carcinoma. E. J. RANKE, S. S. PRESLEY and P. H. HOLINGER. *J.A.M.A., Vol. 182, No. 5, Nov. 3, 1962.*

Tracheogenic carcinoma has a much lower incidence than bronchogenic carcinoma, and its occurrence rate has not increased with the same rapidity as has bronchogenic carcinoma. Early diagnosis of tracheal neoplastic obstruction is usually obscured and delayed by the absence of physical findings and the lack of definitive pathologic signs on routine chest x-ray examination. Persistent wheezing, a hacking cough, and certainly the appearance of occasionally blood-streaked sputum are indications for bronchoscopic examination in spite of a negative chest x-ray film. The comparison of inspiration and expiration chest x-ray films, the lateral x-ray film of the chest, and finally planographic studies of the trachea are additional means that will reveal tracheal obstruction. Obviously, tracheoscopic and bronchoscopic studies give direct visual information which also permits biopsy proof of the neoplastic nature of the lesion. Surgical resection procedures and cobalt-60 therapy have improved the effectiveness of treatment of tracheogenic carcinoma.

Surgical Therapy for Dupuytren's Disease of the Foot. With emphasis on Proper Placement and Design of Skin Incision. J. W. Curtin. *J. Pl. & Reconstr. Surgery, Vol. 30, No. 4, Nov. 1962.*

The same disease process causing the typical hand deformity (Dupuytren's Contracture) is seen in the foot but its surgical therapy is infrequently described. The chief indication for surgery in plantar fibromatosis is discomfort for, unlike the hand, contracture deformity is not a feature. Partial removal of the plantar fascia may lead to an unsatisfactory result and since its removal causes no discomfort excision of the entire plantar fascia is preferred. In contrast to the many skin incisions for exposure of the palmar fascia the literature has almost nothing to guide one in the surgical approach to the plantar surface of the foot.

This paper acquaints the reader with the indications for surgery in plantar fibromatosis and demonstrates how one arrives at the proper skin incision which will allow adequate exposure without jeopardizing skin flap.

New Aids for Diagnosis of Insulin-Secreting Tumors. T. B. Schwartz, F. A. dePeyster and R. K. Gilchrist. *Arch. Surg. 85: 166-172, July 1962.*

The differential diagnosis of a patient with an insulin-secreting tumor of the pancreas usually is not difficult in the presence of repeated low fasting blood sugar values, aided by other standard tests. However, when borderline fasting blood sugar values are encountered, it may be difficult to distinguish insuloma from other non-operative hypoglycemic conditions, particularly those of early diabetic and functional origins.

It was the purpose of this report to describe the response of proved insuloma patients to L-leucine and tolbutamide which, when administered under these latter conditions served as useful differential diagnostic adjuncts. Confirmation of a diagnosis of insuloma may also be obtained.

Thirty minutes after the administration of 150 mg. of oral L-leucine per kilogram body weight, a marked hypoglycemic accentuation ranging from 21 to 76% below fasting blood sugar values were observed in patients with insulin secreting tumors in contrast to patients with functional hypoglycemia and early diabetes where no significant effect was noted. After insuloma removal, no reaction to L-leucine was observed.

I.V. administration of 1 gm. sodium tolbutamide likewise provoked marked hypoglycemia in patients with insuloma which persisted for a long as three hours. Tolbutamide administration only slightly depressed blood sugar levels in patients with prediabetic hypoglycemia and in healthy subjects.

Anomalous Origin of Left Coronary Artery from Pulmonary Artery. M. H. Agustsson, B. M. Gasul, E. H. Fell, J. P. Bicoff and D. F. Waterman. *J.A.M.A. 180:15, 1962.*

Anomalous origin of the left coronary artery from the pulmonary artery was observed in three children. The anomalies in two, 6 and 7 years of age, were of the adult type, characterized by minimal symptoms, a continuous murmur at the left sternal border, and left ventricular hypertrophy. Retrograde aortography demonstrated a dilated and tortuous right coronary artery draining via an extensive collateral circulation into the left coronary artery and on into the pulmonary artery. Ligation of the left coronary artery at its origin resulted in immediate and sustained improvement in these patients.

The anomaly in the third child, 16 months of age, was of the infantile type, characterized by marked symptoms in early infancy, the absence of murmurs, marked cardiomegaly, and electrocardiographic evidence of left ventricular strain or myocardial infarction. Retrograde aortography demonstrated a dilated right coronary artery, but poor collateral circulation and no definite shunting into the pulmonary artery. This child died 8 days following ligation of the left coronary artery.

A review of the literature is presented. The anomalies are divided into infantile and adult types by the extent of the collateral connections between the right and left coronary arteries. Myocardial blood flow may be significantly improved in the adult type by ligation of the left coronary artery. The absence of collateral circulation in the infantile type suggests the necessity of anastomosis of the left coronary artery to a systemic artery or the aorta to establish an adequate left coronary blood flow.

Erythrocythemia in Primary Carcinoma of the Liver. M. A. Escobar, F. E. Trobaugh, Jr.: *A.M.A. Archives of Internal Medicine, Vol. 110, No. 3, September, 1962.*

During a prolonged period of observation, a 50 year old colored man developed concomitantly an elevated red cell count and hepatic carcinoma. The increased red cell count was characterized by an increased red cell mass, and normal plasma volume, white blood count, platelet count and arterial blood oxygen saturation. There was no splenomegaly. Such occurrence has been described in eighteen Chinese cirrhotics in Hong Kong and in one patient in the United States. It seems that carcinoma of the liver must be added to the other tumors and diseases which are associated with non-hypoxic erythrocythemia. These include carcinoma of the kidney, hydronephrosis and cerebellar hemangioblastoma.

Symptoms & Signs of Peripheral Arterial Disease. G. deTakats. *Med. Clin. N. America. 46:3, May, 1962.*

In evaluating the signs and symptoms of peripheral arterial disease as aids in delineating vascular syndromes, the following points may be made in telegraphic style:

1. CONGENITAL VASCULAR ANOMALIES. Symptoms appear at birth, or in the first few years. Affected limb longer, larger, covered with one or several birthmarks. Tortuous, huge veins carry red, oxygenated blood. Bruit over fistulas usually absent. Heart usually not enlarged. Repeated attacks of phlebitis or lymphangitis. Trauma, puberty and pregnancy accelerate the extension of the lesion.

2. ARTERIAL TRAUMA. Clear-cut history of injury followed immediately, but at least within three weeks by swelling, discoloration, mass, abnormal pulsation or palpable thrill and audible bruit. Pulsations may be weak or absent below the injury. Concomitant venous, lymphatic or nerve injury may be present. Angiogram can reveal the site of an aneurysm, pulsating hematoma or arteriovenous fistula. The site of the loudest and highest to-and-fro murmur localizes the arteriovenous communication.

3. ARTERIAL INFLAMMATION. The source of bacterial, viral and allergic arteritis may be looked for. Thromboangiitis obliterans, rheumatic arteritis and panarteritis, all belong in this category. The segmental lesions of occlusion or microaneurysms may be in the small arteries, often in the veins, seldom—and only by extension—in the major vessels. Periods of exacerbation and remission are common. Arterial biopsies are revealing only in the acute stage. Sedimentation rate high, heparin resistance high.

4. ARTERIAL EMBOLISM AND THROMBOSIS. Sudden onset. Embolism frequently multiple, sometimes being the first clinical symptom of silent myocardial infarct. Hemorrhage into popliteal or subclavian atheroma often immediate cause of obstruction. Extremity below occlusion cold, pale, pulseless. Motor paralysis (unable to move toes)

ominous. Gradual spontaneous improvement by release of vasospasm and increase in collateral circulation.

5. ARTERIOSCLEROSIS OBLITERANS. Most frequent of all the chronic occlusive diseases. Gradual, insidious onset by narrowing, kinking, rigidity or plaque formation.

Melanotic Progonoma in Childhood. R. Medenis, D. P. Slaughter and T. K. Barber. *Pediatrics, 29:600, 1962.*

Melanotic progonoma, a rare tumor frequently referred to as "retinal anlage" tumor, is peculiar to infants. This tumor usually originates in the maxilla. It is differentiated microscopically by a typical tissue pattern and the presence of pigment. Cases of tumor have been reported under a variety of names, such as melanoma, melanocarcinoma and melanotic progonoma. 25 cases of melanotic progonoma have been reported in the literature. In 23 of these cases the tumors originated in the maxilla or mandible, in 1 in the area of the anterior fontanelle, and in two at extracephalic sites. Despite the fact that melanotic progonoma is a tumor peculiar to childhood, only one case has been reported in a pediatric journal. The article describes another case of melanotic progonoma of the maxilla in a five-month old infant that was successfully removed surgically, and there has been no recurrence after one and one-half years. The origin of this tumor is unknown. It is benign and amenable to surgery. It is therefore important that cases be recognized early in childhood to insure optimal therapy.

The Excretion of Organic Anion in Renal Tubular with Particular Reference to Citrate. R. E. Dedmon and O. Wrong. *Clin. Sci., 22:19, 1962*

In renal tubular acidosis the kidneys are unable to form as acid a urine as they can normally; the excretion of titratable acid is therefore reduced. Frequent additional features are excessive renal loss of bicarbonate and reduced excretion of ammonium. Patients with a marked deficit in total hydrogen ion excretion usually develop a hyperchloraemic acidosis, but in other patients the inability to excrete hydrogen ion as titratable acid is compensated for by an increased excretion of hydrogen ion in the shape of ammonium, which prevents the development of acidosis—an "incomplete" form of syndrome (Wrong and Davies, 1959). The present study was undertaken to obtain additional data on the urinary excretion of citrate and other organic anions in patients with renal tubular acidosis, both without treatment and after long-term alkali therapy. For purposes of comparison we have studied normal subjects, and patients with other forms of nephrocalcinosis, chronic renal disease and potassium depletion. The results of these studies lend support to the concept of a renal tubular defect in citrate production as a causal factor in the production of the nephrocalcinosis of renal tubular acidosis, but they do not support the concept of diminished urinary citrate as a cause of other forms of nephrocalcinosis. Treatment of renal tubular acidosis with alkalies increased citrate excretion but did not return it to normal, which suggests that the reduced urine citrate of this disease is not the result of intracellular acidosis alone. Urinary citrate was measured in six patients with renal tubular acidosis and compared with data from normal subjects and patients with other forms of renal disease, including other forms of nephrocalcinosis. In normal subjects the rate of citrate excretion was related to urine pH, being increased in alkaline urines and reduced in acid urines. In renal tubular acidosis citrate excretion was markedly reduced, both in absolute terms and in relation to urine pH. Long term treatment with sodium and potassium bicarbonate, in doses sufficient to correct acidosis, increased urine pH and citrate excretion slightly, but in no case did the relationship between these two variables become normal. The excretion of citrate was normal, or only slightly reduced, in three patients with nephrocalcinosis resulting from hypercalciuria and in two patients with chronic glomerulonephritis and reduced glomerular filtration. Citrate excretion was reduced in two potassium-depleted patients. The excretion of some other organic anions and amino-acids in renal tubular acidosis was also studied. Paper chromatography showed no gross abnormality. However, in the one patient in whom quantitative measurements of urine keto acids were performed there was a reduced excretion of d-ketoglutarate and a slightly increased excretion of pyruvate. In renal tubular acidosis diminished citrate excretion did not appear to be the result of a systemic or intracellular acidosis alone, but may be more intimately related to the disturbed tubular function. The findings were consistent with the hypothesis that a reduced excretion of citrate is a causal factor in the nephrocalcinosis of renal tubular acidosis, but suggest that diminished citrate excretion plays no part in the etiology of the other forms of nephrocalcinosis studied.

Effect of Hypervitaminosis D on Serum Factors in the Rabbit. R. EISENSTEIN, R. DEDMON and A. HEMMENS. *Proc. Soc. Exp. Biol. & Med. 109:482, 1962.*

Hypervitaminosis D is usually associated with changes in the levels of calcium or phosphate in the blood serum. It is often tacitly assumed that abnormal levels of these ions in the blood are responsible for the widespread soft tissue calcification associated with this disease state. A study of the calcific lesions in rabbits with hypervitaminosis D, however, revealed that there are characteristic patterns of distribution of these lesions which cannot be explained by this assumption alone and indicated that the lesions were related to local variations in susceptibility of tissue to the effects of excessive Vit. D. To clarify the matter, it seemed desirable to study the state of the calcium and phospate in the serum of these animals. An electrophoretic study of the serum was also done to determine if there was a change in the serum protein pattern. Inasmuch as elevations of serum muco-proteins have been described in rat hypervitaminosis D, hexosamine levels were also determined. Hypervitaminosis D in the rabbit induced widespread calcification of many organ systems unaccompanied by changes in concentration of calcium, ultrafiltrable calcium, citric acid or hexosamine in the serum. With a high dosage level, there was a conspicuous increase in serum level of inorganic phosphate, presumably secondary to renal damage. At a low dosage level where there was minimal renal damage and no change in the serum inorganic phosphorus or calcium, widespread soft tissue calcification occurred. These data indicate that, in the rabbit with hypervitaminosis D, metastatic calcification is not necessarily due to hypercalcemia or hyperphosphatemia. The vitamin induced an unexplained rise in level of B-2 globulin, a fraction split from the B-globulin when $CaCl_2$ is added to the electrophoresis buffer.

STATEMENT OF INTENT

Near the middle of Chicago spreads the vast complex of medical and allied institutions called the West Side Medical Center—the largest of its kind in the world. Presbyterian-St. Luke's Hospital with a capacity of approximately 1,000 beds is the only private voluntary hospital in this complex.

The Presbyterian-St. Luke's Hospital has traditionally held that optimum patient care results in an institution where teaching is an obligation. The private practitioner may teach on his patients or those of his colleagues or on the large number occupying the service wards. He teaches medical students from the University of Illinois and he teaches the many house officers. Their curiosity, and aggressiveness and their spirit of intellectual competition, serve to sharpen the thinking and skills of teacher and student alike.

However, teaching what is known is not sufficient. An institution to progress must search for newer truths; unless an atmosphere of inquiry prevails mental apathy results. For these reasons the considerable resources of the hospital have long been directed toward numerous research projects.

This then is our intent—to publish the results of the combined endeavors of this medical and scientific staff—the staff of a large metropolitan hospital, uniquely placed, dedicated to the care of people and engaged in teaching and research.

PRESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN

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RUBEOLA IMMUNIZATION WITH INACTIVATED MEASLES VACCINE

Robert A. Behmer, B.S.
Charles E. Bell, A.B.

INTRODUCTION

Many physicians, as well as the lay public, regard measles as one of the "nuisance" diseases many children are destined to acquire before they enter school. Coupled with this is the belief that measles is a "benign" condition. Therefore, attempts to eradicate measles will most likely be met with a considerable degree of apathy.

That measles can be a devastating disease, however, was shown in the 1951 epidemic in Greenland. The outbreak was accompanied by a mortality rate of 1.8%. Fortunately, subsequent epidemics in Greenland have had a lower mortality.[1] The United States has experienced a decline in the mortality rate from 7 to .2 per 100,000 over the period from 1912 to 1959.[2] It should be stressed, however, that measles causes more deaths than any other common childhood contagious disease.

The morbidity rate in the United States has declined little, if at all, in the last 50 years. The rate in 1912 was 300 per 100,000 and 250 per 100,000 in 1959.[2] Figure 1 illustrates the reduction in the mortality rate and the relative stability of the morbidity rate.

The major complications of measles are otitis media and bronchopneumonia, due to secondary bacterial infection, and encephalitis and viral pneumonia due to the measles virus itself.[3] Our present armamentarium provides ready means of dealing with the bacterial complications. However, adequate therapy is lacking for the treatment of the viral complications. Measles encephalitis, the most serious complication, is seen in about one of each one thousand cases and often leads to death or permanent central nervous system damage.[4] Of those not receiving antiserum in the 1951 Greenland epidemic, five per one thousand developed encephalitis.[1]

We have then, in measles, a disease of considerable morbidity, sometimes accompanied by severe complications, and with an occasional mortality. Above all it is a disease that can be prevented. It is the purpose of this paper to discuss our efforts in this direction.

CLINICAL TRIAL

During the summer and fall of 1962 an immunization study against measles was conducted in the Well Baby Clinic of Presbyterian-St. Luke's Hospital. Inactivated vaccine was utilized which was prepared from the Edmonston strain of the measles virus.*

Children were considered eligible for vaccine administration if they met all of the following criteria: (1) Between the ages of 6 months and 5 years (2) No past history of rubeola or gamma globulin administration (3) No recent exposure (1 month) to rubeola by history (4) Would not require other immunization proce-

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From the Division of Pediatrics

*This was generously supplied by Chas. Pfizer & Co., Inc., who also assayed the sera for neutralizing antibodies.

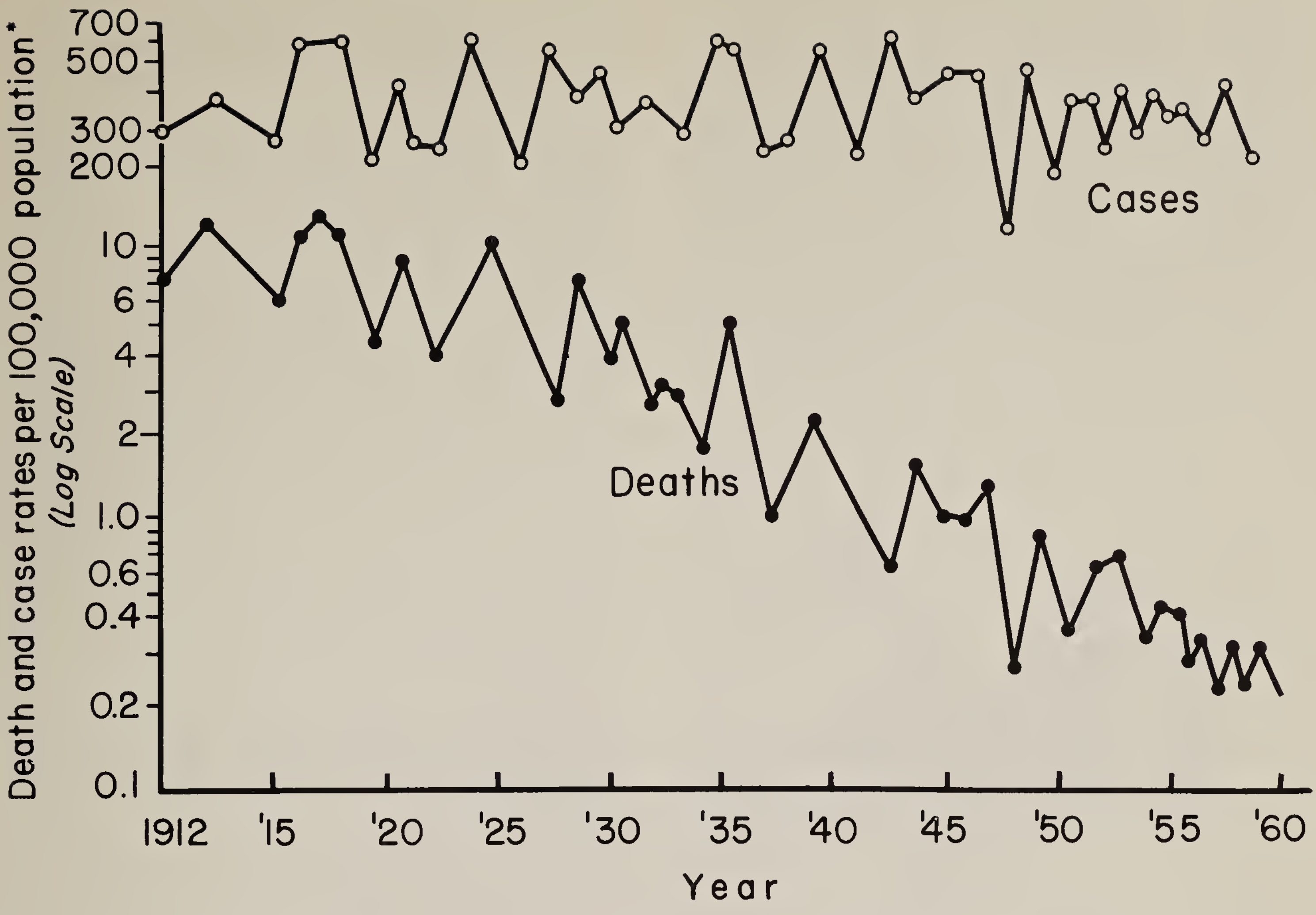

Fig. 1.—Case and Death rate of measles from 1912 to 1960. *From Langmuir[2]

dures during the time the study was to be conducted.

Having fulfilled these criteria, the children were started on an immunization schedule which consisted of three 0.5cc intramuscular injections of the inactivated vaccine at approximately monthly intervals. Venous blood samples were drawn the day of the first injection.

Ninety-two children were started in the program and 50 (54%) were able to complete the program. These 50 children received three injections, had pre-inoculation neutralizing antibody titers of less than 1:4, and had post-inoculation blood drawn. Of those children not finishing the study (42), twenty-one (50%) were found to possess seriologic immunity. Twenty (48%) were excluded for lack of attendance or lack of a suitable blood sample. One child was excluded because she developed, following exposure to measles, a febrile illness with clinical signs suggestive of measles between the second and third injections.

Figure 2 illustrates the age distribution of the children who were found to be serologically immune in the absence of a past history of clinical measles.

Three of the four children under the age of one year, who were serologically immune, completed the series. It was felt that their immunity may have repre-

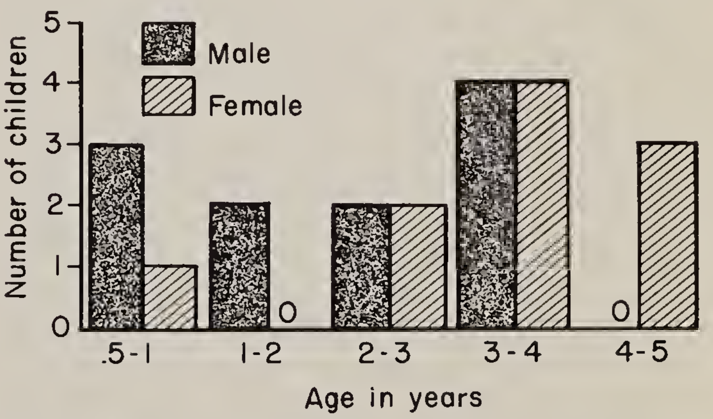

Fig. 2—Age distribution of 21 serologically immune children.

sented transplacentally acquired antibodies. In one study[11], 27% of 44 infants had antibody titers greater than 1:10 at 3 months of age. Ninety-three percent of the 44 infants were born to mothers with titers of greater than 1:10 at birth. Antibody titers were not determined in the mothers of children in our study.

Figure 3 illustrates the age distribution of the 50 children who took part in the complete study.

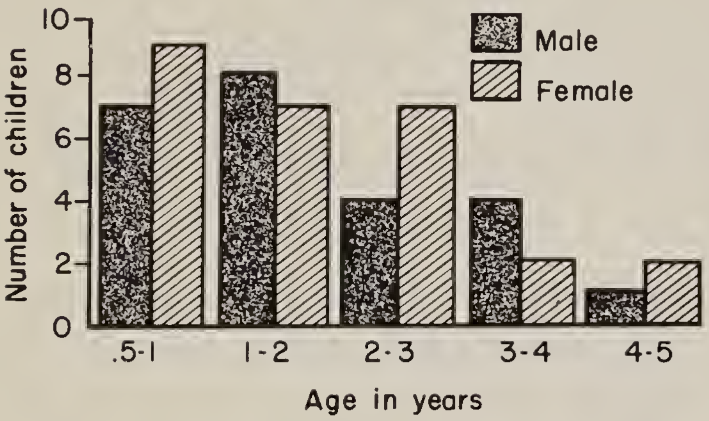

Fig. 3—Age distribution of 50 children completing the study.

The interval between the first and second injection ranged from 24 to 45 days, with a mean value of 29.9 days and a mode of 28 days. The range between the second and third injection was 21 to 60 days, with a mean of 31.5 days and a mode of 28 days.

Post-inoculation titers were drawn 14 to 28 days after the third injection. The mean interval between the last injection and the drawing of the blood sample was 16.6 days, the mode being 14 days.

RESULTS

Children were considered to have developed serologic immunity if their post-inoculation antibody titers were 1:8 or greater. This meets National Institute of Health standards for determining conversion. The conversion rate was 92% (46 patients). Four children (8%) had a titer of less than 1:8 and were therefore, considered non-converters.

The incidence of side reactions as ascertained by questioning on return visits, was minimal. Eight reactions were observed in a total of 221 injections. Six consisted of a mild temperature elevation on the evening of the injection. One child experienced a moderate temperature elevation approximately 6 hours after inoculation, followed by a transient macular rash of the face and back of two days duration. The other child, who was allergic to sulfa and penicillin, experienced a moderate temperature elevation of two days duration, after the first injection. This was followed by the appearance of nummular eczema of both lower legs. Although it was felt that the skin eruption was not related to the vaccine, no further injections were given to the child.

DISCUSSION

The challenge to produce an effective means for the prevention of measles is being met. As with other viral diseases, two basic avenues of approach are open: passive and active immunization.

Passive Immunization: Gamma globulin has been employed in attempts to prevent or attenuate an attack of measles. It is difficult to protect contacts because exposure usually goes unnoticed, and to be effective gamma globulin must be given within seven days of exposure. The end result obtained, attenuation or prevention, varies with the dose of gamma globulin administered.

Immunization with gamma globulin is impractical on a large scale. The immunity provided is of short duration (about six weeks) and multiple injections may be required. The high cost, too, is an important factor to be considered in all large scale immunizations.

Active Immunization: Active immunization provides the best means of preventing measles. This may be conferred by the administration of either the live virus (attenuated) vaccine or the killed virus (inactivated) vaccine. This method has been successful in other viral and bacterial diseases. The optimal way to achieve active immunity, however, is in question. There is a controversy at this time over the use of the live virus vaccine and the killed virus vaccine, just as there is a controversy over the Sabin (live) vs. the Salk (killed) poliomyelitis vaccine.

The development of the tissue culture technique by Enders has provided a means of growing the measles virus. The Edmonston strain of the virus, isolated in 1954,[5] has been investigated in both the attenuated and inactivated forms.

In one study,[6] the attenuated strain produced a serologic response, after one injection, in 96.7% of 311 children. The pattern of response was not unlike that seen in the natural disease. A modified rash was noted in 45% by the 11th day, and 20% experienced a fever in excess of 103°F. No central nervous system or bacterial complications were noted and the modified disease was not contagious. Ninety-five children in the group did not develop measles, in spite of known exposure, for periods ranging up to 21 months.

Attempts to reduce the side effects of the attenuated vaccine by simultaneously giving gamma globulin have been successful. In a study by Krugman, et al.[7] febrile responses in excess of 101°F were reduced from 94% to 40% and the incidence of rash from 56% to 8%. The percentage of children developing immunity, however, fell from 96.5% to 90.5%. A more recent trial[8] using gamma globulin simultaneously has demonstrated a 99% serologic response and a similar reduction of side effects. This was made possible by the administration of higher doses of vaccine. One hundred percent protection following exposure has been noted in this group over a one year period.[9] The antibody response following the administration of the attenuated virus, with or without gamma globulin, parallels that seen in the natural infection. Namely, the neutralizing antibodies persist while the compliment fixation antibodies diminish.[6,7]

The attenuated vaccine appears to be contraindicated in children with acute leukemia because of the possibility of developing a fatal giant cell pneumonia. In a small series of children with acute leukemia, one child developed this complication. However, attempts to isolate the virus, post-mortem, from the lung have not been successful.[10]

The alum precipitated, formalin inactivated Edmonston strain, the vaccine used in our study, has been noted to produce an adequate serologic response in 72% to 100% of children after three injections.[11,12] The side effects observed with the killed vaccine have been minimal; local tenderness, erythema, and a mild temperature elevation have been observed in a small percentage of children.[11] The immunity produced by the killed vaccine is capable of protecting the individual against natural measles and against the side effects of the live virus vaccine.[12]

Insufficient data are present at this time to evaluate the duration of the immunity produced by the killed virus vaccine. It has been proposed that this vaccine may be permanently effective. The incubation period of measles may be long enough to allow for a recall response and ample opportunity exists for repeated contact with the virus.[13]

It appears then, that the *attenuated* virus vaccine is very effective in producing a serologic response, but its administration is accompanied by undesirable side effects, unless combined with gamma globulin. The *inactivated* virus vaccine, although not as consistently effective in producing a serologic response, is accompanied by fewer and less severe side effects.

SUMMARY

Inactivated measles vaccine was administered to 92 children ranging in age from 6 months to 5 years. Twenty-one of the 92 were found to possess serologic immunity in the absence of a past history of measles or exposure to measles. Fifty of the remaining 71 children completed the series of three injections. Forty-six (92%) converted to serologic immunity, four children (8%) failed to convert. The incidence of side reactions was minimal.

We are indebted to Dr. H. G. Bucheleres for his assistance in carrying out this study and in the preparation of the manuscript.

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ASSESSMENT OF INFANTILE HYDROCEPHALUS

David Yashon, M.D.
Oscar Sugar, M.D.

When confronted with an infant with a too-rapidly enlarging head four questions usually come to the mind of the clinician. Is the diagnosis hydrocephalus? What is its etiology? What is the optimum treatment? What is the infant's prognosis? We will attempt to deal with these questions in this sequential order.

DIAGNOSIS

There are several clinical features which should alert the clinician to the diagnosis of hydrocephalus. The head may appear large; the eyes are frequently turned down; the scalp veins may be prominent. Increased intracranial pressure should be suspected in cases of infants who fail to feed well, infants who fail to achieve normal growth and development, and in infants who have other congenital anomalies particularly involving mid-line structures, for example meningocoele and encephalocoele. Palpation of the fontanelles invariably reveals them to be tight and bulging and the cranial sutures are felt to be separated. X-ray of the cranial vault reveals split sutures.

The most accurate method of determining whether or not an infant has a too-rapidly enlarging head is by direct mensuration. A too rapidly enlarging head can be established immediately in most cases but in others frequent serial follow-ups may be required. Most present day pediatric reference tables are inadequate as a standard of head size because they fail to give frequent references as to head size during the first few weeks of life. If the early diagnosis of infantile hydrocephalus is to be made, adequate reference tables are vital. Also measurements with regard to prematurely born infants are important since a disproportionately large number of these infants become hydrocephalic later. O'Neill's[1] tables fulfill these requirements. (Figures 1,2,3)

Two other causes for a too-rapidly enlarging head in infants are subdural hematoma following trauma and subdural effusions occurring after pyogenic meningitis. The trauma can occur at birth or later but no history may be obtainable. Both of these diseases may masquerade as the syndrome of infantile

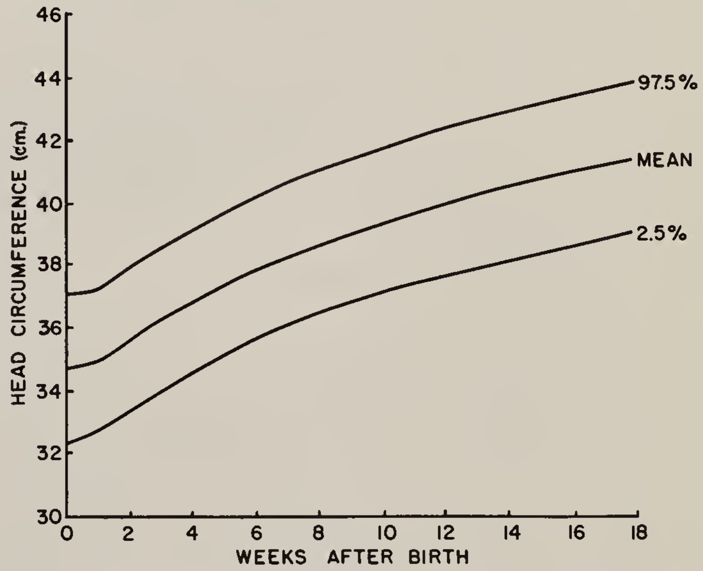

Fig. 1.—Head circumference/age chart for full-term babies; 95% limits for head circumference with respect to age.
From: O'Neill, E. M.[1]

From the Department of Neurosurgery

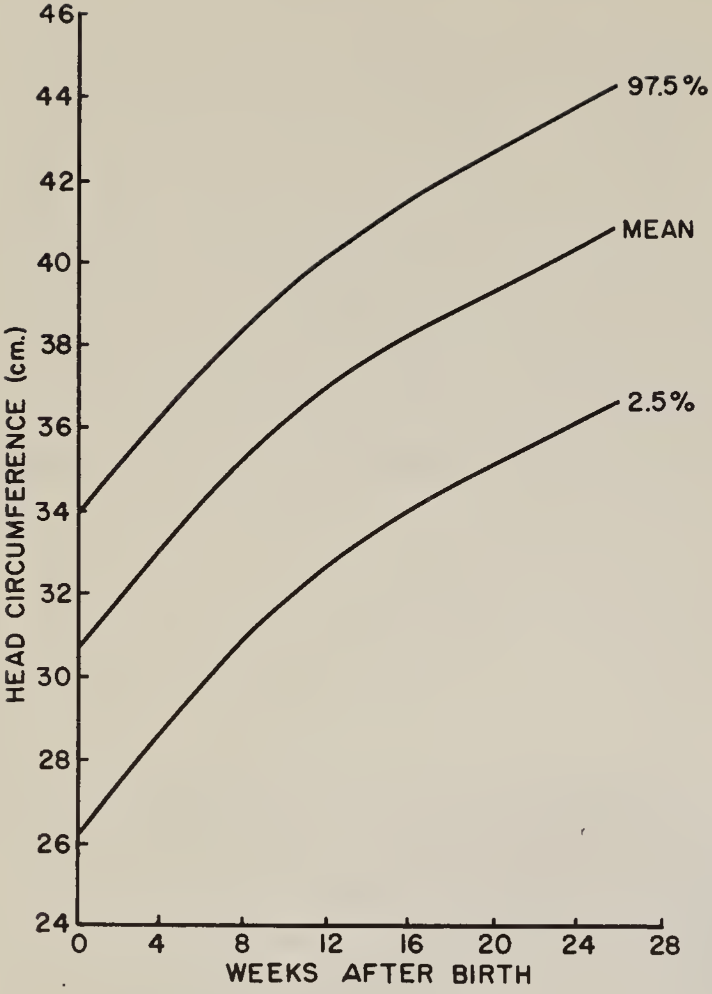

Fig. 2.—Head circumference/age chart for premature babies; 95% limits for head circumference with respect to age.

From: O'Neill, E. M.[1]

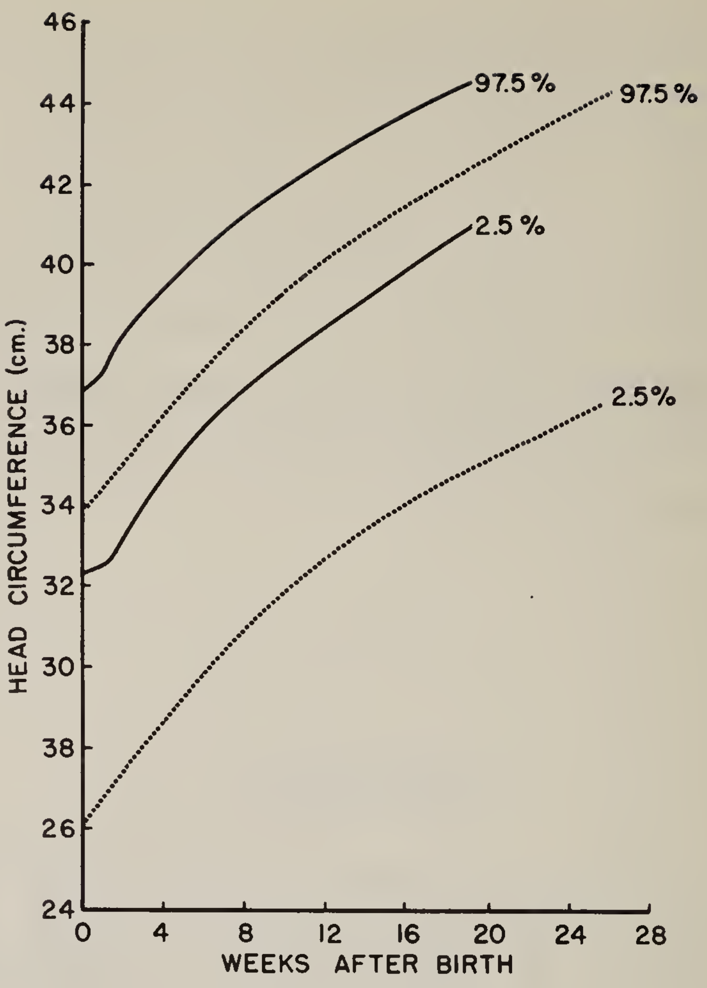

Fig. 3.—Graphs from Figs. 1 and 2 shown together for comparison; solid line: range of normal head circumference values for full-term infants; broken line: range of normal head circumference values for premature infants.

From: O'Neill, E. M.[1]

hydrocephalus. The diagnosis of these two entities can be made by bilateral subdural taps. The tap into the subdural space is performed at the most lateral border of the anterior fontanelle. In the case of the hematoma the fluid is usually blood tinged. In the subdural effusion the fluid is xanthochromic. It is imperative that the diagnosis of these subdural collections be made since the management is entirely different from that of infantile hydrocephalus.[3,4]

In addition to bilateral subdural taps other diagnostic studies that may be performed are: (a) dye test using indigo carmine: Five milliliters of this dye are instilled into the lateral ventricle. In communicating hydrocephalus a lumbar puncture should reveal the dye to be present in the lumbar subarachnoid space in 20 minutes or less. In most cases of obstructive hydrocephalus the dye cannot be obtained from the lumbar subarachnoid space. Communicating hydrocephalus implies a block in the basal cisterns, whereas in obstructive hydrocephalus the block is in the foramina of Monro, aqueduct, or fourth ventricle. Both communicating and obstructive hydrocephalus are considered internal hydrocephalus. A too-rapidly enlarging head due to subdural collections can be considered external hydrocephalus.

(b) "bubble" study: 20 cc of air are introduced into each lateral ventricle and the child positioned so that the ventricles can be outlined. A space occupying lesion may be demonstrated and cortical thickness may be determined in this manner. Most observers feel that cortical thickness is not a good indicator of prognosis.[5,6] With the latest methods of surgical treatment of hydrocephalus these two studies are of academic interest only in many cases, but occasionally a tumor is found even in a newborn infant. Using some ingenuity, however, these three diagnostic procedures may be performed together if necessary.

ETIOLOGY

The etiology of infantile hydrocephalus is multiple. Laurence[2] studied 100 cases of infantile hydrocephalus at post mortem. (Tables 1 and 2) Congenital malformation alone accounted for 46%, 50% of patients had infections and 4% of patients had tumors. With regards to the site of block 50% had isolated sites, 48% had multiple sites while two infants had no block but had "oversecretion" of cerebrospinal fluid. This implies the possibility of a choroid plexus papilloma. Children with congenital malformations are more prone to infection than normal infants. Post-natal intracerebral bleeding or infection may cause either isolated or multiple blocks secondary to adhesions. There may be no antecedent history of trauma or infection.

OPTIMUM TREATMENT AND PROGNOSIS

With no treatment at all, 40% to 50% of hydrocephalic infants show spontaneous arrest. Laurence[7] followed 182 untreated children with the syndrome of infantile hydrocephalus. Of 81 whose hydrocephalus underwent spontaneous arrest, 41% showed normal intelligence. We have followed for two years or longer 58 patients with this syndrome, who did not have surgical therapy. Of these 58

TABLE 1

ETIOLOGY OF HYDROCEPHALUS

Malformations		46
Alone	14	
With infection	30	
With trauma	2	
Inflammation		50
Infection alone	17	
Trauma alone	22	
Unknown (probably infection or trauma)	11	
Tumours		4
		Total 100

(After Dr. K. M. Laurence)

TABLE 2

SITE OF BLOCK CAUSING HYDROCEPHALUS

(100 Post-mortem Examinations)

Isolated sites		50
Aqueduct	10	
Fourth ventricle foramina	7	
Basal cistern block	21	
Arnold-Chiari malformation	12	
Multiple sites		48
Basal cistern block, with block at foramina of Monro, aqueduct or fourth ventricle	20	
Arnold-Chiari malformation, with blocks at foramina of Monro, aqueduct, fourth ventricle or basal cistern	28	
No block (over-secretion)		2
		Total 100

(After Dr. K. M. Laurence)

patients 31 are living. Of the 31, 13 were considered to have already undergone spontaneous arrest when first seen. About one third of this non-surgical group are considered near normal in intelligence while the remainder are mentally retarded.

Numerous surgical approaches, both experimental and clinical, for drainage of cerebrospinal fluid from the ventricles or other areas of the subarachnoid space to various body cavities have been attempted. Most early reports have been quite enthusiastic but as time passes the enthusiasm has waned. Some of those we have used include ventricular and lumbar subarachnoid peritoneostomy, ventricular and lumbar subarachnoid ureteral shunts, the "Torkildsen" operation of ventriculocisternostomy, extirpation of the choroid plexuses, ventriculo-Fallopian and lumbar subarchnoid-Fallopian tube shunts. By and large these procedures have met with success only in isolated cases and in the hands of a few surgeons.

Forty-two patients have been surgically treated by us with one or more of these older procedures. Ten patients are still living. Of those living, 3 had bilateral choroid plexectomies, 2 infants had third ventriculostomies, 1 had a lumbar subarachnoid ureterostomy, 1 had a lumbar subarachnoid peritoneostomy, 1 had a lumbar subarachnoid Fallopian tube shunt, 1 had a "Torkildsen" procedure, and 1 had had a posterior fossa exploration with lysis of adhesions. Most of these patients are mentally and physically retarded. It is evident that the overall success rate of these procedures is less than if the patient had not been treated at all.

In the last five years ventriculo-venous shunting has been used with much greater apparent success. The technique of ventriculo-venous bypass was attempted as early as 1908 and 1911 by Payr.[8,9] Ventriculo-venous bypass was successfully developed by Nulsen and Spitz[10] in 1952, and Pudenz et al.[11] in 1957. At present there are commercially available the highly developed Spitz-Holter and Pudenz-Heyer one way valve shunts. These permit ventriculo-venous drainage between the lateral ventricle and venous system (as represented by the jugular vein and right atrium) using polyethylene tubing.

Several authors mention prognosis of patients with ventriculo-venous shunts. Carrington[12] stated that 43 of 50 patients have functioning shunts after a 2 to 18 month follow-up. Ten revisions were necessary in eight patients. Anderson[13] reported that in 20 of 36 patients the hydrocephalus was controlled. Macnab[5] stated that in 98 of 140 patients the valve was functioning well. All of the five cases of Grotte and Lundberg[14] have been successful. This is a total of 166 (70%) successful cases out of 231. Russell[15] also put forth the 70% success figure in his 33 cases. This surgical procedure has the advantage of simplicity over older techniques. The technical aspects are well presented in the literature.[5,14]

We have followed 46 patients with the ventriculo-venous shunts for periods of from about one to four years. Thirteen of these patients have died. Of 33 who have surgically arrested hydrocephalus 23 are normal to near normal in mental development, while ten are retarded. 23 revisions were necessary in the group of 46. In terms of life or death, which is up to now the only objective measurement we have of the success of a given series, this again is a 70% success rate.

DISCUSSION

From available statistics it would appear that a form of ventriculo-venous shunt is of value in the syndrome of infantile hydrocephalus. If no treatment at all is attempted, between 40% to 50% of the patients survive. If a form of ventriculo-venous shunt is used the survival rate is increased to 70%. We recognize the fact that revisions and even removal of the shunt may be necessary. In these cases the temporary arrest is of benefit to the patient and further progression of the disease may cease. The fact is that with present day therapy arrest of hydrocephalus can be accomplished early. Early arrest, of necessity, decreases morbidity, a parameter which is difficult to evaluate.

Another problem with regard to a given case of hydrocephalus is the question of arrest or progression of the disease. Schick and Matson[16] answer the question generally. They feel that some cases of slowly progressive hydrocephalus may masquerade as arrested hydrocephalus. Arrest is considered to occur only if: a) further head growth ceases altogether until growth of the child catches up to the size of the head, after which head

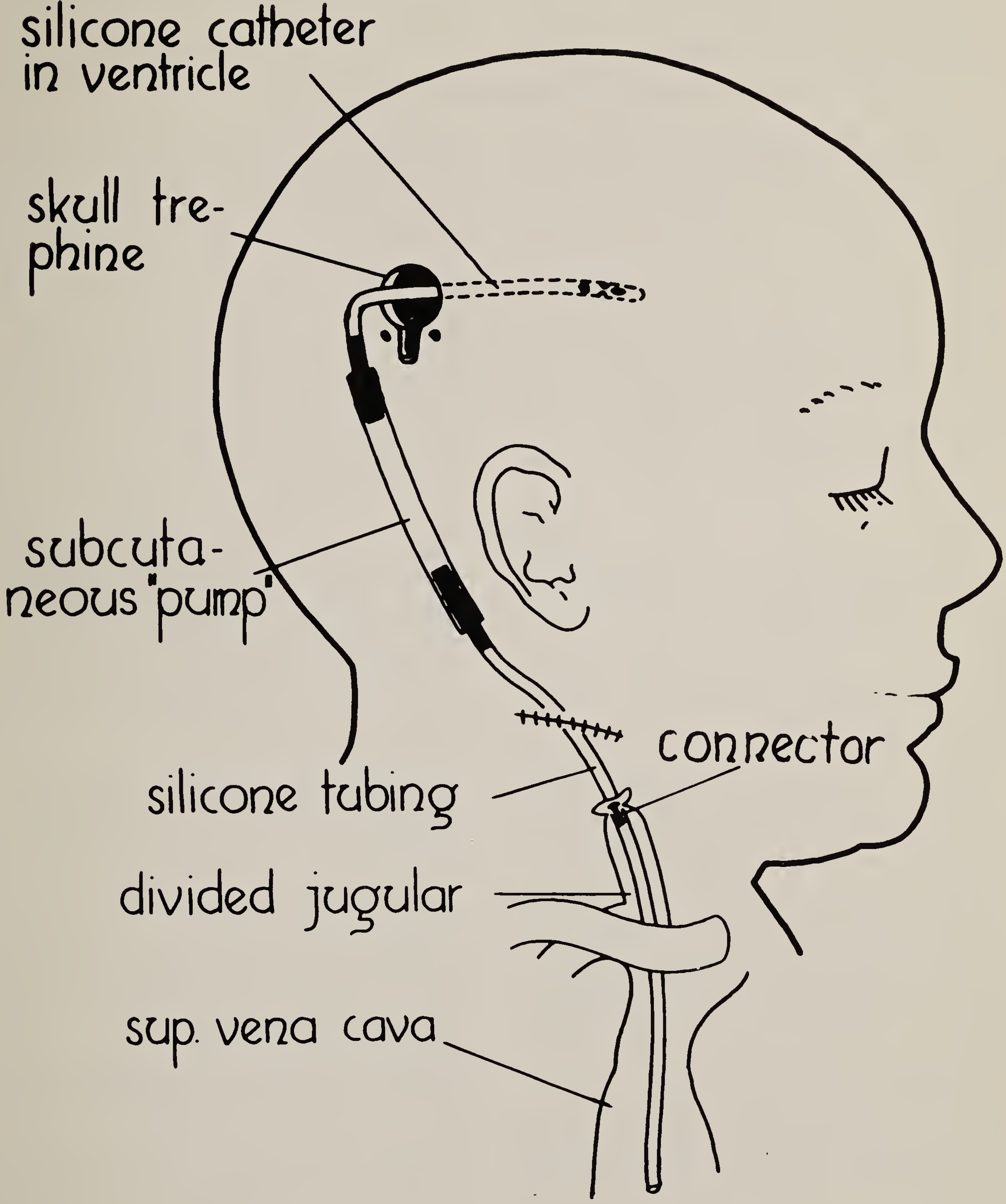

Diagram of Spitz-Holter Ventriculo-Atrial Shunt.*

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*Courtesy, The Holter Company, Bridgeport, Pennsylvania growth is resumed at a normal rate, and b) the head actually becomes smaller after surgical or spontaneous arrest. If a young infant, an already enlarged head should not continue to grow at all until the body size has caught up with the head size if arrest is truly present. Not acceptable for inclusion in the definition of arrested hydrocephalus is the case in which the rate of growth of the head decreases but continues steadily so that it parallels the normal growth curve while still remaining above it. The exact criteria of arrest can only be met by frequent serial head measurements.

This paper deals only with the first objective criterion of success of a procedure, namely the life or death of the patient. It has not been possible to obtain a second, more exact, criterion of success—namely, assured arrest of hydrocephalus. The well-being of patients the ultimate criterion of success is yet to be achieved.

SUMMARY AND CONCLUSIONS

A summary of current concepts in the field of infantile hydrocephalus is presented. It appears that the most effective surgical treatment at present is a form of ventriculo-venous shunt. Only 10 of 42 patients having other types of operative treatment survived. Using the Pudenz-Heyer or Spitz-Holter valves, 33 of 46 patients survived. With no surgical treatment, 31 of 58 patients had spontaneous arrest of their hydrocephalus with 13 of these already having an arrest when first seen. The conclusion that may be drawn from both our cases and the recent literature is that a form of ventriculo-venous shunt should be attempted in all cases of hydrocephalus as early as possible. This procedure offers the patient a 20% to 30% decrease in mortality, and an appreciable decrease in morbidity when surgical arrest is achieved early in life.

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ATTITUDES TOWARD PROBLEMS OF PATIENT MANAGEMENT: A Study of Senior Medical Students

David I. Cheifetz, Ph.D.
Jack Saporta, Ph.D.
Paul E. Nielson, Ph.D., M.D.

For the past few years we have been studying the process of teaching senior medical students in a clerkship setting. We have not been primarily concerned with the problems of communication and retention of factual content, but rather with the area of attitudinal development and change in medical students. This paper reports part of one of the studies in which we have been interested.

The clerkships we have worked with most intensively are psychiatric, although for certain control purposes we have also used others. The psychiatry clerkships studied are not designed to develop technical psychiatric competence or skills. Rather, they have as a primary goal the continuing development of such understanding and attitudes in the student as will enable him to deal more comfortably and effectively with the medical patient, regardless of the nature of his illness.

METHOD

One of the evaluation techniques we have used is an attitude scale devised for the purpose of measuring the strength of various attitude complexes in physicians and medical students. When administered at the beginning and end of a clerkship experience, the scale enables us to make inferences concerning the nature and strength of some pre-clerkship attitudes and the effect the clerkship has on such attitudes.

Briefly, the scale consists of 50 items, the majority of which make affirmative statements regarding ways of dealing with specific doctor-patient problems. Each item is responded to by choosing one point on a six-point continuum ranging from Strongly Agree to Strongly Disagree. The points on this continuum are weighted so that a score can be assigned the response to each item and a total score derived. Items were selected and standardized by using a criterion group of 60 experienced psychiatrists. A large pool of items was constructed, the attempt being to devise items which tapped or reflected attitudes important in the doctor-patient relationship. A group of judges examined the pool of items, and those items were retained which elicited agreement among the judges as to attitude-relevance, clarity and appropriateness. The retained items were administered to the criterion group of psychiatrists for final selection. Items judged suitable for final inclusion in the scale were those which elicited responses in the same direction from at least 85 per cent of the criterion group. The assumption was made that attitudes held in common to this extent by the criterion group were attitudes we would wish developed in students. As the scale is

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From the Section of Psychology,
Department of Psychiatry

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finally used with students, responses in the same direction as those of the criterion group are deemed to be desirable and constructive and to reflect positive attitudes; responses which are contrary are deemed to reflect a less desirable approach. By the split-half method, reliability coefficient of the scale is 0.76. Administration of the scale to representative groups at the pre-medical level, at each year level of medical school, and to residents, indicates that there are regular and significant total score increments as the student progresses through medical training.

Subdivision of the scale by item analysis yields six clusters of items reflecting different attitudes:

I. Flexibility of Approach—A tendency to individualize relationships with patients rather than being bound by rigid and predetermined sets.

II. Physician's Reactions—An awareness that the physician as a person will often have emotional reactions to his patient and the problem being treated, and that the effectiveness of the physician is often related to a recognition of his own feelings toward the patient.

III. Medical Authoritarianism—A tendency to develop omnipotent ways of dealing with people based on a perception of the medical role as providing a superior and privileged status personally and socially.

IV. Patient's Feelings Toward Illness—An awareness that recognition of the patient's emotional reaction to his illness is often a necessary condition for effective management of the illness.

V. Patient's Feelings Toward Physician—An awareness that the physician must strive to be cognizant of and willing to deal with the patient's personal and emotional reactions toward him.

VI. Whole Person Concept—An awareness of the interrelationship, for management purposes, of the physical illness presented and the personal, social and cultural aspects of the patient's life.

To date this scale has been administered to some 800 individuals at different levels of training and experience. This paper reports a sub-study of 75 senior medical students serving a psychiatric clerkship which is held five half-days a week for a period of six weeks. The scale was administered during the first and last sessions of the clerkship and was similarly administered during the same period to a non-psychiatric clerkship control group at the same institution. Compared with the psychiatry clerks, students in the non-psychiatric clerkship were from the same population, at the same level of medical training and spent an equal amount of time in their clerkship. We were concerned with the attitudes manifested by our students and the changes which might occur in them over a brief period of time.

RESULTS

1. Comparing pre-clerkship with post-clerkship results, the psychiatry clerkship group demonstrated a significant shift in attitudes in the positive or desired direction. Mean total scale scores improved to a degree significant at the 1% level of confidence. (Figure 1) 22 of 50 scale items moved significantly in the positive direction. No scale item showed a significant negative shift.

2. During this same period and at the same institution, the non-psychiatric clerkship control group, which was essentially identical at pre-testing, did not show a similar significant change from pre-testing to post-testing, either in mean total score or in total number of items that moved in the positive direction. (See Figure 1) Seven of 50 scale items showed a significant positive shift; two showed a significant negative shift.

3. Concerning separate attitude categories for the psychiatric clerkship groups: (Figure 2)

(a) Two of the six attitudes (Physician's Reactions and Whole Person Concept) appear to be well established initially. Their mean scores of 4.55 and 4.64 respectively place them clearly in the positive range of response, with 85% of the students falling in this range.

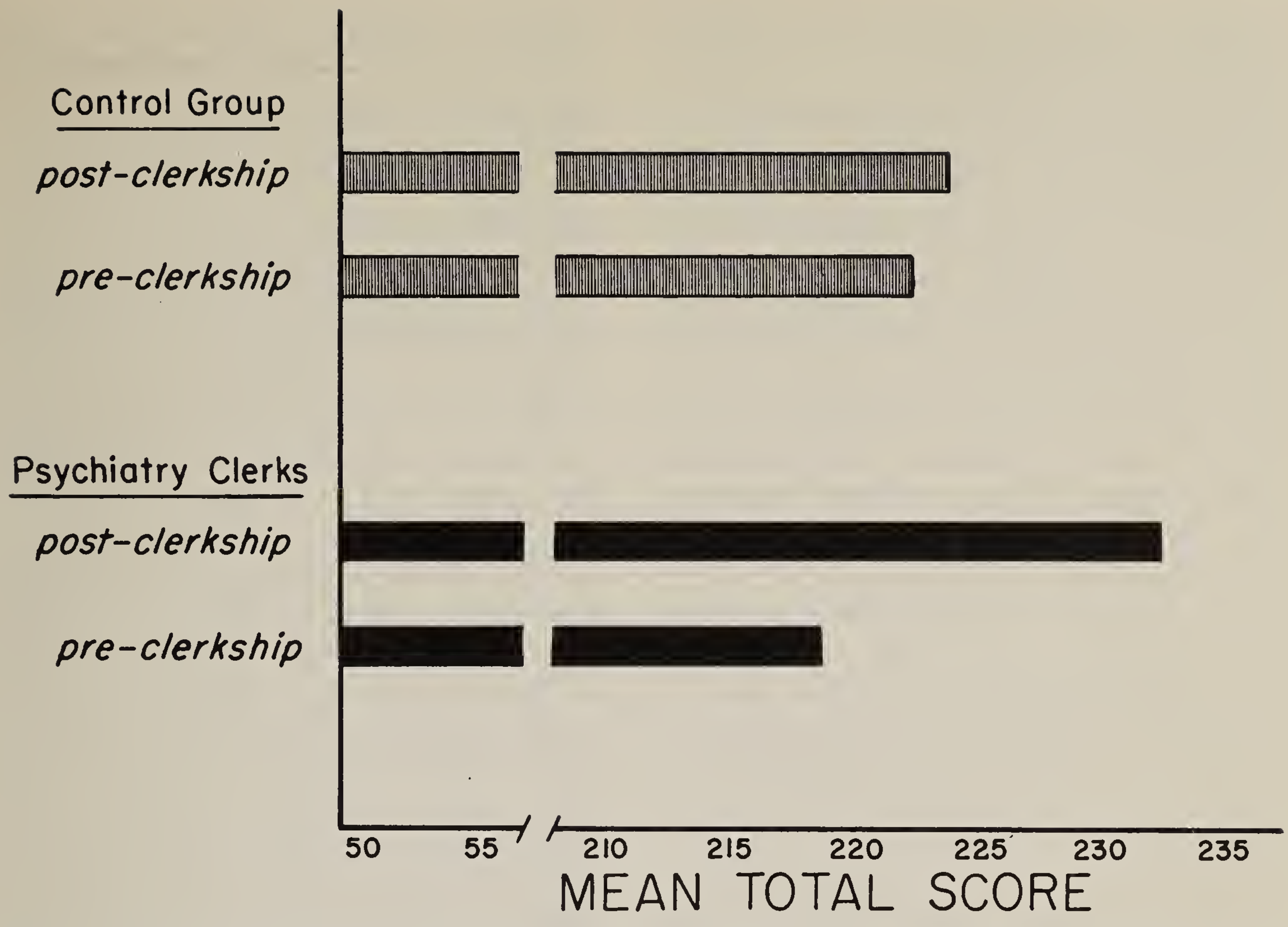

Fig. 1.—Pre to post change in mean total EGAP scores; psychiatric vs. non-psychiatric clerkship groups.

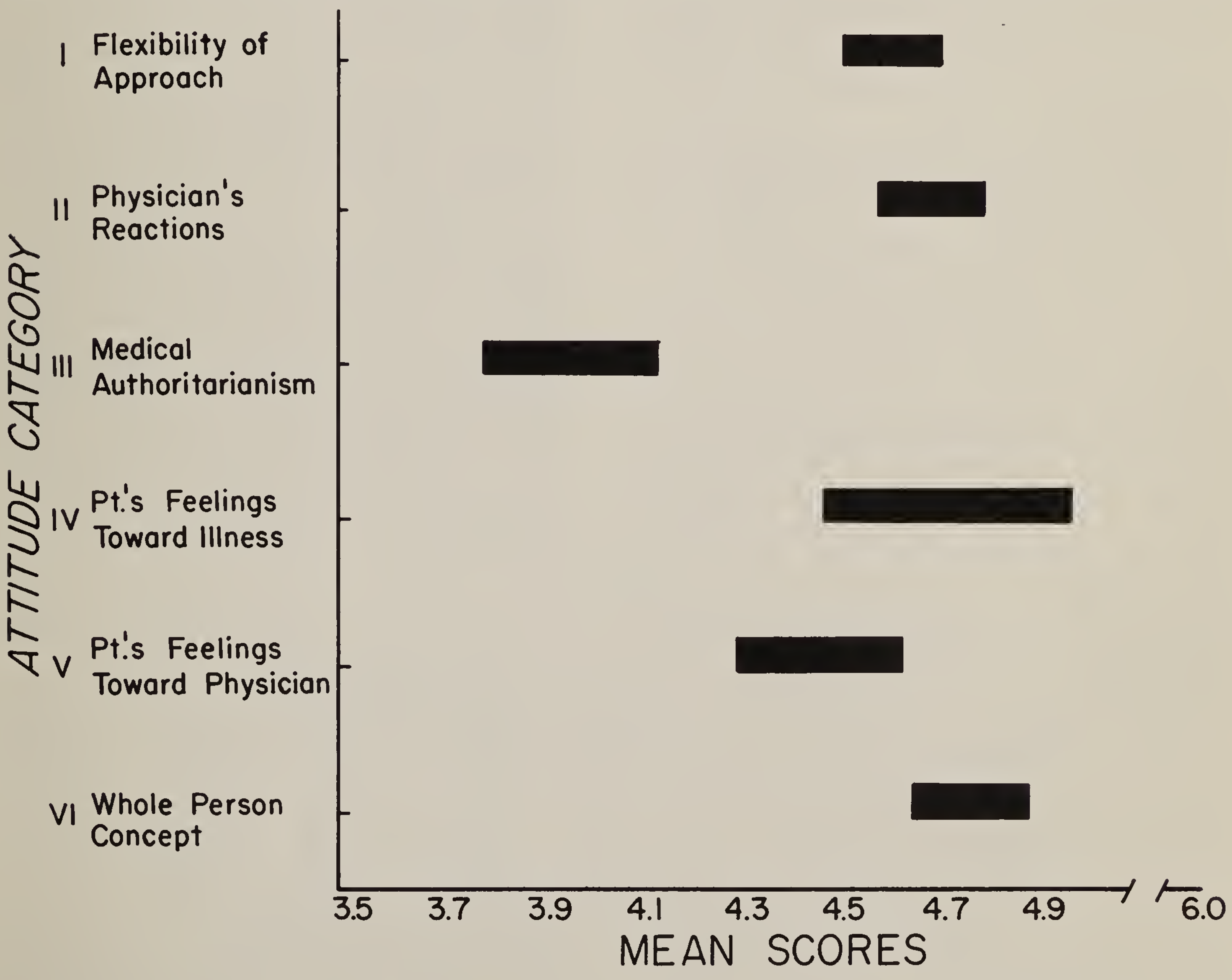

Fig. 2.—Pre to post change in attitude category mean scores, psychiatric clerkship group.

One attitude category, Medical Authoritarianism, reflects an undecided group response initially. Mean score for the category is 3.78, placing it close to the mid-point of the Agree-Disagree continuum, and almost 40% of the students score in the negative direction.

(b) Although attitude categories differed in degree of amenability to change, five of the six reached a final status in which 80% to 90% of student opinion is in the positive direction, with attitudes strongly held. The attitude category reflecting awareness of patients' emotional reactions toward illness showed the greatest positive movement, both in terms of increased strength with which the attitude is held and increased percentage of student agreement. The amount of change in this category exceeded that shown in other categories by ratios as high as 3:1.

(c) At the close of the clerkship, the category Medical Authoritarianism still exhibited the lowest percentage of students responding in the desired direction, their mean score reflecting only mild agreement with the premise of the criterion group.

Table 1 summarizes mean scores, differences and significance of differences for the psychiatric clerkship group.

DISCUSSION

What then do these data seem to indicate? Let us begin with some of the more positive aspects. If we view the combined attitude complexes studied as a unitary function—*i.e.* in terms of total scale scores — we see that a relatively brief but intensive clerkship experience can produce significant gains of the sort we hope for. That these are probably a product of the specific emphases found in the psychiatry clerkship and not necessarily the simple result of such clinical experience as occurs in any clerkship is suggested by the finding that an equal exposure to a non-psychiatric clerkship produces no significant attitudinal changes of the sort measured.

But there is not really a uni-dimensional positive attitude structure of the sort referred to. The approach we hope to encourage in dealing with the patient as his physician is a complex one made up of many attitudes, and our scale as a whole taps not one but a number of these. Through item analyses we can consider some of these attitudes more or less singly, and certain questions can be asked. Which of the attitudes studied seem most positively established by the time the medical student reaches his fourth year? Which attitudes are, from our viewpoint, more negative? Which seem most amenable to change in the clerkship experience and which tend to be refractory?

As reflected by our scale, students initially appear to hold positive attitudes in five of the six areas studied. However, in terms of the strength with which these are held, or the commitment apparently indicated, only two of the five seem strong enough to be clearly unequivocal. One is the attitude reflect-

TABLE 1

Attitude Category	Description	Pre-Mean	Post-Mean	Mean Difference	t	p
VI	Whole Person Concept	4.640	4.849	+.209	4.359	<.001
II	Physicians' Reactions	4.551	4.786	+.235	3.377	<.02
V	Pt.'s Feelings Toward Physician	4.291	4.614	+.323	3.231	<.05
III	Medical Authoritarianism	3.775	4.121	+.346	2.662	*
I	Flexibility of Approach	4.486	4.695	+.209	2.594	*
IV	Pt.'s Feelings Toward Illness	4.450	4.946	+.496	2.520	*

*Approach significance at p = .06 to .07 level of confidence

Table 1.—Changes in attitude category mean scores, psychiatric clerkship group.

ing the idea that medical treatment involves an appreciation of the individual in his total social and psychological milieu and not as an isolated biological organism—the so-called Whole Person Concept (Figure 2, Category VI). The other is an attitude indicating awareness that the physician's emotional reactions toward his patient can be important in treatment (Figure 2, Category II).

The three attitude clusters which are also in the positive range initially, but more weakly so, deal with the importance of recognizing the patient's emotional reaction to his illness, his emotional reaction to his physician, and the importance of individualizing approaches to patients (Figure 2, Categories IV, V, I). These are three areas, therefore, which might deserve special emphasis in dealing with the student.

If we examine these five attitude areas in terms of their change during the clerkship experience, the results indicate that those which were firmly established to begin with remain firmly established, and those which were held more ambivalently at the outset become established at a significantly higher and firmer level. Not all attitude areas improve equally. Alertness toward the importance of recognizing the patient's emotional reactions to his illness increases more than any other attitudinal factor, occuring at the close of the clerkship as the attitude eliciting the widest and strongest agreement. This area will be recognized as one receiving particular emphasis in most psychiatric clerkships today. One would hope that it might be an area of significant gain for students, and it is gratifying to see that this does occur.

On the basis of these positive findings one might feel fairly sanguine about student performance. Our students reach their fourth year with certain desirable attitudes toward problems of patient management, and it is possible to improve these even further in the course of a brief clerkship. One sees an increasing awareness on the students' part that they as physicians have both positive and negative reactions to patients which may influence the nature and course of treatment. Students become much more aware of the importance of dealing with patient's emotional reactions toward their illness, and they view with less favor the notion that formality, impersonality and studied detachment are necessary accoutrements of the scientific physician. Finally, students broaden their concept of the meaning of illness and the potential influence on etiology, course and treatment of emotional factors, family attitudes, environmental milieu, etc. From this description the educator might well conclude that his world is rosier than he had perhaps thought.

However, there is an attitudinal area which appears in our data and casts a shadow over any atmosphere of excessive optimism. This is the area which seems to reflect the student's view of himself as occupying an authoritarian, omnipotent role *vis a vis* the patient. It reflects the student's acceptance of the idea that he has unquestioned prerogative to influence, manipulate or control the patient's behavior because of his own special status as physician, and that this prerogative gives him free license to override the patient's judgment as he sees fit and impose his own value system upon him.

We have assumed such qualities to be largely negative in the development of a good physician. Yet, of all areas measured, this is the single one in which our fourth year students as a group register a neutral reaction. While they hesitate to openly espouse such an attitude, neither are they able to reject it. In the course of the clerkship some significant gain is made in counteracting this system of operation, but even so this area remains the most negative of all those studied, at best eliciting only mild agreement with the hoped for position.

We regard this rather seriously, because it seems to us that such an investment in physician omnipotence must interfere with the degree to which the student can behave in a manner consistent with his other, more positively expressed attitudes. For example, our students indicate awareness that their patients' emotional reactions toward the doctor-patient relationship must be understood if the relationship is to be an effective one. Yet, if the student has such a large stake in the protection of an omnipotent, unchallengeable role, how can he possibly deal constructively with the challenging, questioning, resistive and puzzling problems which arise in all relationships and are emphasized in the doctor-patient relationship?

The question of medical omnipotence as a personal attitude has often been discussed. The contribution to its development of four years of training which necessarily stress the great responsibility our society accords the physician is generally understood. One might also question the degree to which choice of a medical career by the student, and choice of the applying student by the medical school, operate selectively to give us students whose personalities easily accept the omnipotent role.

Such explanations aside, we were also struck by the possible defensive nature of such a role in the students we studied. Our students were in the midst of an intensive clinical experience which, like most clerkships, certainly confronted them with the anxiety of bearing real responsibility for real people. They were also on the verge of leaving the shelter of the medical school for the even greater personal responsibility which internship and practice entail. It requires no great disposition toward psychological explanations to suggest that recourse to omnipotence is an easy defense against an exacerbation of self-doubt and concern over lack of competence. If this is so, however, we might be well advised to pay closer attention to such a development by being more alert to the reactions of our students as they begin personally to face the problems of medical responsibility. It might be possible through such alertness to help the student recognize his own anxiety more fully and find more constructive ways of dealing with it. We do not suggest that this is an easy task. We do suggest that it is a task which calls for attention by medical educators.

INTEREPIDEMIC HOSPITAL STAPHYLOCOCCAL INFECTIONS

John Burnside, B.S.
Helen MacLean, M.S.
Dieter Grüneklee, Cand.Med.
Friedrich Deinhardt, M.D.
Edward J. Beattie, Jr., M.D.

INTRODUCTION

After the introduction of a reporting system of all wound infections at our hospital it became evident that sporadic infections were numerically more important than epidemic outbreaks. Previous studies have been primarily concerned with epidemics or outbreaks attributable to a single vector which generally were caused by a single bacteriophage type Staphylococcus.[1-5]

We decided, therefore, to study interepidemic staphylococcal infections. Specifically, we were interested in determining; (1) the percentage of our patients who were *admitted* with coagulase positive *Staphylococcus aureus*, (2) the percentage of our patients who contracted Staphylococci *during* their stay in the hospital and (3) the efficiency of our aseptic techniques.

MATERIALS AND METHODS

All cultures were taken with sterile cotton-tipped swabs and immediately placed in Difco thioglycollate broth and incubated for 6 hours at 37 degrees C. From these cultures Bacto-Blood-Agar base plates with 5% defibrinated human blood were seeded, streaked, and incubated at 37 degrees C. for 12 to 18 hours. Colonies were picked from these blood agar plates and Gram stained. All Gram positive cocci were inoculated into BBL trypticase soy broth and incubated at 37 degrees C. for 8 to 12 hours. Three drops of these cultures were then added to .5 ml of Bacto-Coagulase plasma, incubated at 37 degrees C. in a water bath, and read at 1 and 4 hours for coagulation.

All coagulase positive Staphylococci were bacteriophage typed on Bacto nutrient agar plates using routine test dilutions of 29, 52, 52A, 79, 80, 3A, 3B, 3C, 55, 71, 6, 7, 42E, 47, 53, 54, 73, 75, 77, 83, 42D, 81 and 187 bacteriophage. The tests were read after 24 hours incubation at 30 degrees C. Staphylococci which did not type were retested using 1,000 times the routine test dilution.

Ninety-one surgical patients were selected to reflect the general admissions, with respect to age, sex, surgical service and location within the hospital. Swabs from the nose, perineum, skin and wound were cultured at intervals.

EXPERIMENTAL RESULTS

Swabs from the nose and perineum from 40 of the patients were taken within 12 to 20 hours and from 51 within 4 hours of admission. From table 1 it can be seen that the percentage of patients harboring Staphylococci did not increase within the first 4 to 20 hours.

Cultures were repeated 48 hours after the first culture, every 4 days thereafter and at discharge. As can be seen in table 2, 51.6% of the studied patients remained free of Staphylococci during their entire stay at the hospital, whereas 17.6%, although negative on admission, yielded 1 or more positive cultures at some time during their hospitalization. Generally, Staphylococci were found in cultures from the nose or from the nose and perineum and only one patient yielded consistently positive perineal cultures in the absence of Staphylococci in the nose.

TABLE 1

	No. pos. for Staph.	%
51 patients first cultured within 4 hours of admission	17	33.3
40 patients first cultured 12–20 hours after admission	11	27.5

Table 1. Comparison of the incidence of *Staphylococcus aureus* in nose and perineal cultures immediately after admission and after 12–20 hours of hospitalization.

TABLE 2

Status of Patients	No.	%
Positive on first culture	28	30.8
Negative on first culture and positive some time later	16	17.6
Negative throughout hospitalization	47	51.6

Table 2. Results of Serial Cultures for *Staphylococcus aureus*

TABLE 3

Status of Patients	No.	%
Negative on admission but became carriers	5	5.5
Constant carriers	18	19.8
Constant carriers with a strain change	2	2.7
Total	25	27.5

Table 3. Per cent of *Staphylococcus aureus* carriers

Defining a carrier as one who gives at least 3 positive cultures of the same bacteriophage type Staphylococcus with not more than 1 negative culture in the interim, the carrier rate was found to be 27.5% and most of these were already carriers at the time of admission to the hospital. (Table 3)

The effect of previous hospitalization was investigated and it was found that of the 28 patients who were positive on admission 18 (64.4%) had been hospitalized within the previous year.

Cultures of the skin of the operative site just prior to operation were taken to give an index of the organisms on the skin before surgery. After scrubbing with soap and water the skin was again cultured. Immediately before dressing the wound after surgery, a third culture was taken to measure the effect of the bacteriocidal agents applied and the degree of extraneous contamination during the operation. At no time was the skin found to be sterile before scrubbing. Table 4 summarizes the numbers of types of organisms found on the skin after scrubbing and before dressing. Table 5 summarizes the different organisms found.

Table 6 shows that the per cent of anaerobic or microaerophilic organisms isolated from the skin surface increased after surgery. This suggests that these organisms which normally reside in the deeper layers of the skin are brought to the surface as a result of the scrubbing and the surgical incision.

Cultures were also taken of the wound at each dressing change. Of 7 patients who became symptomatic for a Staphylococcus wound infection, 5 had carried the organism before the day of surgery. Each of these 5 had the same bacteriophage type Staphylococcus in the wound as they had carried nasally previous to surgery. (Table 7)

Table 8 summarizes the cases in which Staphylococci were isolated from the wound. Of these 13 cases, 7 developed a clinical wound infection. In 5 instances Staphylococci were isolated from the operative site before or immediately

TABLE 4

No. of patients	Number of types of organisms after scrubbing			Types of Preparation	Number of types of organisms before dressing		
	0	1	2 or more		0	1	2 or more
1	0	0	1	Ether, Tinct. of Zephiran, Ethyl alcohol	0	0	1
1	0	0	1	Ether	0	0	1
4	1	2	1	Ether, Tinct. of Zephiran, Ethyl alcohol	0	1	3
1	0	0	1	Iodine and Tinct. of Zephiran	1	0	0
10	1	8	1	Tinct. of Zephiran	1	6	3
4	0	3	1	Ethyl alcohol	0	2	2
6	0	4	2	Aqueous Zephiran	2	3	1
9	—	—	—	Tinct. of Zephiran (No scrub)	1	3	5
4	2	2	0	Iodine and Ethyl alcohol	2	0	2
5	0	2	3	Nothing	0	2	3
45	4	19	10	TOTAL	7	17	21

Table 4.—Numbers of different types of organisms found on the skin at different times during surgery.

TABLE 5

Organisms Isolated	Before Scrubbing	After Scrubbing	Before Dressing
Staphylococcus aureus	2*	3	3
Staphylococcus albus	34	12	21
Enterococcal Streptococcus	9	1	2
Viridans Streptococcus	3	0	1
Peptostreptococcus	2	1	3
Gamma Streptococcus	1	2	1
Hafnia sp.	1	0	0
Micrococcus sp.	6	6	7
Diplococcus sp.	0	0	2
Pseudomonas sp.	0	1	0
Bacillus sp.	5	0	1
Anaerobic Diphtheroids	1	5	12
Proteus sp.	1	0	2
Escherichia coli	1	1	1
Clostridium sp.	6	2	0

Table 5.—Types of organisms isolated at different times during surgery.

*Frequency of isolation

after the operation and twice Staphylococci were first isolated from the wound during a later dressing change.

Phage typing of all coagulase positive Staphylococci isolated during this study revealed no common strains.

DISCUSSION

The high percentage of patients who demonstrated Staphylococci on the first culture (30.8%), the high carrier rate (27.5%) and the low rate of wound infections (7.6%) indicate that the clinical syndrome of infection is the exception rather than the rule even in Staphylococcus positive patients. However, 5 out of 7 clinical wound infections occurred in Staphylococcus carriers which indicates the higher probability that these patients may get a wound infection.

TABLE 6

	Before Scrubbing		Before Dressing	
	Aerobes	Anarobes	Aerobes	Anaerobes
No.	63	9	40	15
%	87.5	12.5	72.8	27.2

Table 6. The change in the relative numbers of anaerobes before and after surgery.

Although patients hospitalized within the past year show a higher incidence of Staphylococcus than those who had not been hospitalized, we suspect this to be more the result of prolonged debility rather than actual exposure to a hospital environment because no common bacteriophage type Staphylococci could be demonstrated.

TABLE 7

			Staphylococci in wound	
Staphylococci isolated initially:	No.	Staphylococci never in wound	No clinical infection	Clinical infection
Before surgery	18	9	4	5
At time of surgery	2	0	1	1
After surgery	2	0	1	1

Table 7.—Staphylococcal wound infections in relation to the time Staphylococci were first isolated.

TABLE 8

Staphylococci Isolated From:							
	Cultures before surgery		Skin at surgery			Wound at dressing change	Clinical infection
Case No.	Nose	Perineum	Before scrubbing	After scrubbing	Before dressing		
1	+	—	—	—	—	+	+
2	+	—	—	+	+	+	+
3	+	+	+	—	+	+	+
4	—	+	—	—	—	+	+
5	+	—	—	—	+	+	+
6	—	—	—	—	—	+	+
7	—	—	—	+	—	+	+
8	+	—	—	—	—	+	—
9	—	—	—	—	—	+	—
10	+	—	—	—	—	+	—
11	—	—	+	+	—	+	—
12	+	—	—	—	—	+	—
13	+	—	—	—	—	+	—

Table 8.—Summary of cases with Staphylococcus positive cultures from the skin or wound.

Our data support the implication that autoinfection may be as important, if not more so, as contamination by the surgical team (6-8).

From our bacteriological laboratory an infection rate of 1.5% of all clean surgical cases was reported over the last year. The higher infection rate (7.6%) in this study may be the result of the small sampling and/or it may reflect the practice of treating infections without identifying the causative agent by bacteriological cultures.

Of 45 patients cultured in the surgical theater, none were sterile before scrubbing, and only 7 were sterile before dressing. The efficiency of scrubbing seems to be of more importance than the bacteriocidal agent used, and the utmost attention should be given to the preparation of the surgical field.

Although only 91 patients were studied, all attempts were made to obtain a representative cross-section, and it was our opinion that 91 extensively studied cases were of as much value as many more under less optimal conditions.

This study took place in a private teaching hospital during the months of June through September. The data do not, therefore, indicate whether the etiology of Staphylococcal infection is influenced by seasonal conditions and the sampling while representative for this hospital may not be so for another. A second study of 1,004 cases in this hospital a year later gave essentially identical results (9). Two-hundred and ninety-five or 29.5% of the patients yielded positive cultures on admission and the number of Staphylococcal wound infections was 21 or 2%. Again no common bacteriophage type Staphylococci were found. At least 11 of the patients developing a wound infection had had positive nose or perineal cultures on admission or before surgery. Again, the incidence of a Staphylococcal wound infection was twice as high in Staphylococcal carriers (3.5%) than in Staphylococcal negative patients (1.7%).

The results of both studies warrant attention because they indicate that autoinfections are an important factor in interepidemic hospital Staphylococcal infections and it must be remembered that over the years these are larger in number than epidemic cases.

SUMMARY AND CONCLUSIONS

Ninety-one "clean" surgical patients were studied. Nose and perineal cultures were taken at admission, or shortly thereafter, at 48 hours, every 4 days, and at discharge. In addition, swabs of the skin were cultured, which were obtained in the operating room before and after scrubbing, at the conclusion of surgery and at each dressing change. All *Staphylococcus aureus*, coagulase positive strains were isolated and bacteriophage typed. There was no common type. Thirty per cent of all studied patients yielded positive nasal or perineal cultures on admission and 5 out of 7 wound infections were clearly autoinfections with the same bacteriophage type Staphylococcus which the patient had brought with him to the hospital. Nasal and perineal cultures before extensive elective surgery and appropriate preparation of the Staphylococcus positive patients may reduce the incidence of wound infections and is strongly recommended. In addition, Staphylococci isolated before surgery should be tested for antibiotic sensitivity. This would make possible specific therapy at the first sign of infection because it has been shown that the causative agent is most likely the same organism as previously isolated from the nose or perineum.

The multiplicity of organisms found on the "sterile operative field" makes a re-evaluation and constant check of our preparative technique an absolute necessity.

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REVIEW ARTICLE

DISSEMINATED BREAST CARCINOMA
Some Aspects In Management

Nancy J. Gubisch, M.D.
Samuel G. Taylor III, M.D.

Surgery, radiation, and the alteration of the hormonal environment either by ablation or addition have served as the main channels in the palliation of disseminated breast carcinoma. With the recent surge in the general use of chemotherapeutic agents which has been accelerated by the reported high incidence of regression, the idea of "the newer the better," and the ever-present exasperation that "something must be done," one could easily receive the impression that chemotherapy has replaced some of the older methods.

Since the initial studies, however, it appears that the number of women reported benefited by chemotherapy has steadily declined (figure 1).[1–4] This is a phenomenon which has been shared with the reporting of other modes of therapy (figure 2),[5–9] and is due primarily to the small number of patients, the selection rather than randomization in the earlier series, and the later application of more rigid criteria to what can truly be called a worthwhile objective regression. When the same criteria are applied in defining a chemotherapeutic regression as are applied in a hormonal regression, it becomes apparent that although an individual lesion may show as comparable a decrease in size with chemotherapy as with hormonal therapy, the results with the former, in breast cancer, are not as long lasting and less frequently produce sufficient benefit to the total performance status to be of worthwhile value to the patient.

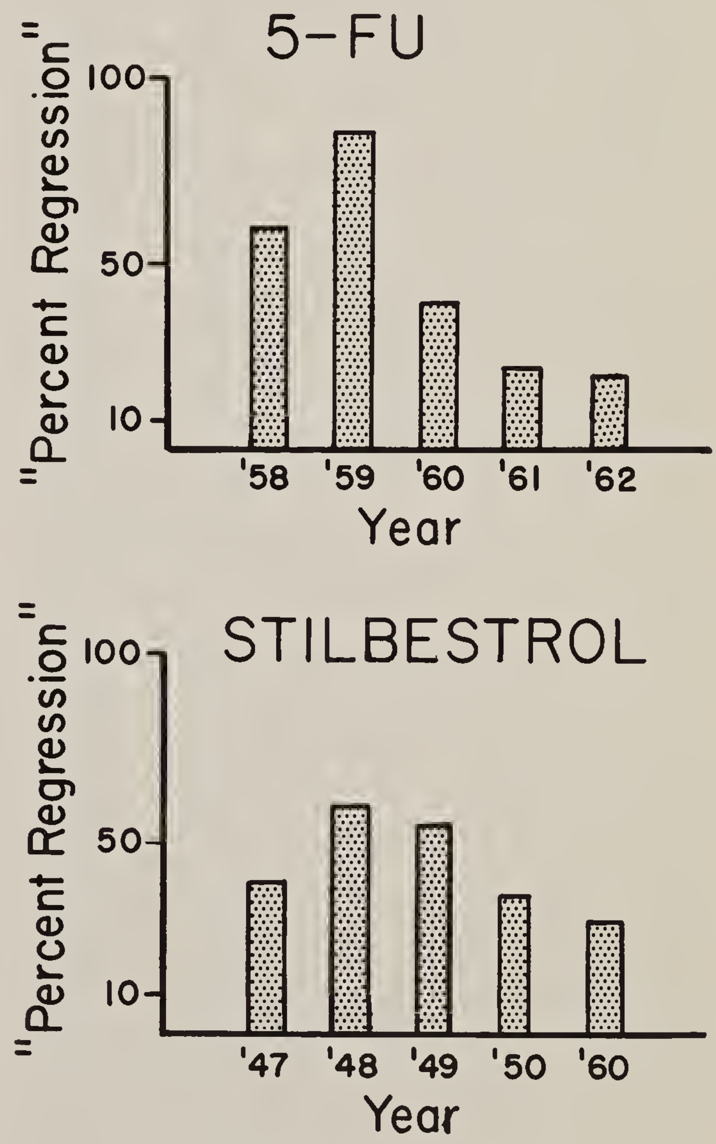

Fig. 1 and 2—illustrate the effect of the later application of more stringent statistical methods and criteria of evaluation on the respective "percent (tumor) regression" noted. One example is taken from both chemotherapeutic (5-Fluorouracil) and Hormonal (Stilbestrol) agents.

From the Section of Oncology, Department of Medicine.

HORMONE THERAPY

The concept of the hormone dependency of tumors, i.e. that the presence of estrogens is necessary to initiate and sustain the growth of mammary carcinoma, can only be demonstrated with assurance in a few strain of mice and one strain of rat.[10–12] Human breast cancer can, at best, be clinically separated into what may be called hormone responsive and non-responsive tumors that are based, in retrospect, on whether or not a favorable regression has been produced by ablative or additive therapy.

Many attempts have been made to relate some aspect of pathology or metabolism to responsiveness. Huggins described all cancers arising from the lobule-alveolar apparatus as "dependent";[13] numerous papers considered urine hormone assays in the pre- and postmenopausal patient before and after therapy;[14] Emerson and Jessiman[15] introduced the "hormone stimulation" and "cortisone inhibition" tests as evaluated by variations of urinary calcium excretion. However, the value of the above observations in predicting responsiveness of tumors to hormonal alteration has been questioned by other investigators. More recently, Hershey[16] has noted as estradiol sensitive transhydrogenase in normal and malignant breast tissue through which the rate of the reduced form of diphosphopyridine nucleotide (DPNH) formation can be quadrupled by the addition of estrogen. Work with radioactive formate and thymidine done at this hospital[17,55] suggests that the percentage of hormone sensitive tumors may be much higher than is clinically evident, and along with in vivo p^{32} uptake studies by others[18] also suggest differential effects of hormones on normal and malignant tissue. A table has been devised by Jull et al[19] correlating breast structure, estrogen and pregnanediol excretion, and response to major ablations. Bulbrooks' studies[20,21] suggest there is a subnormal excretion of 11-deoxy 17-oxosteroids in those women who fail to respond to a major ablation.

Continued research along one of these lines may provide us with a guide in the selection of the "hormone manipulable" tumor. For the present, however, our best method remains an adequate clinical trial after the following generalizations are considered: 1) Menstrual age—in the premenopausal patient ablative procedures are considered first; in the postmenopausal, additive therapy. 2) Previous response to therapy—once hormone responsiveness has been established, subsequent favorable responses are more likely. 3) Site of metastases—soft tissue and visceral lesions respond better to additive therapy, bone lesions to ablative. 4) Disease free interval—the longer the length of time from the initial radical mastectomy to the first evidence of dissemination, the better the chance of a favorable response.

Whether hormonal, or other therapy, has accomplished an increased length of survival—the ultimate measure of effectiveness of therapy—remains unanswered. A woman may live 6 months to 50 years after her initial mastectomy without interval therapy. It is this extremely variable natural history that makes statistical evaluation of any therapy hazardous. We know that those women who respond favorably to therapy will live longer than those who do not, yet this longer survival may be due more to the natural history of the disease than to the response to therapy. With these provisions as a background each mode of therapy will be considered.

Oophorectomy

Whatever the mechanism of effect postulated—be it the withdrawal of some specific stimulating effect of estrogens, the withdrawal of unknown abnormal ovarian hormones, or the alteration in balance of the hormonal environment—it is generally agreed that bilateral oophorectomy is the first mode of therapy to be offered the menstruating and early postmenopausal female with disseminated disease.[22,23] In this and the following section all statistical data will be taken from the recent study by the Joint Committee on Endocrine Ablative Procedures,[24,25] and under "regression" are included only those lasting six months or longer. Oophorectomy can be expected to produce tumor regression in about 30% of cases including those within the first year after the menopause. After this time, unless there is clinical evidence of estrogenic stimulation such as periodic breast engorgement, or a high percentage of cornified cells on exfoliative cytology, this procedure rarely produces a regression. If the patient is younger than 35 years at the time or oopheroctomy her chances of being benefitted will be 16% as compared to 32% if the patient is older than 35 years. Also, if the patient has predominantly soft tissue or bone involvement, her chances of responding will be twice as good than if the main involvement is visceral.

Castration at the time of or shortly after initial diagnosis and treatment of the primary disease as a prophylactic measure is frequently practiced. No well controlled studies on the usefulness of this procedure have been completed.[26,27] A recent study in which oophorectomy cases are randomized against those whose ovaries are left intact is being undertaken. Unless it can be demonstrated that "prophylactic castration" significantly reduces the recurrence rate of breast cancer, castration should be reserved for those cases with recurrent disease. The effect of oophorectomy on measurable tumor is one of the most valuable guide lines for further therapy available at present. The effect of castration performed before metastases are clinically demonstrable naturally could not be measured.

Adrenalectomy-Hypophysectomy

In spite of the variance of hormonal environment that adrenalectomy as compared to hypophysectomy will produce, there appears to be no significant difference between the effectiveness of the two procedures. The choice of the procedure, at present, depends primarily on the experience and interest of the neurosurgical team.[13,27–29]

Because of the attendant morbidity, the necessity for continued replacement therapy and supervision, and the fact that only about 30% of patients will exhibit objective regression, there has been marked conservatism in recommending these procedures. Yet in the individual case the objective regressions that occur have not been surpassed by any other mode of therapy. Unlike oophorectomy there does not appear to be any correlation between menstrual age and response to a major ablation. With an adrenalectomy it is questionable whether the apparent better response in the 40 to 60 age group has any real significance.[30] Of those patients who did not respond to oophorectomy only about 10% will respond to a major ablation. However, a previous favorable response to oophorectomy will increase the chance of a second response to almost 50%. As alluded to in prophylactic castration, one might expect better results if all sources of gonadal and extragonadal estrogen were removed at once; yet combined oophorectomy and adrenalectomy have not proven more effective than the response to each in turn. The place of a major ablation in the palliation sequence is not agreed upon; some prefer it as the next procedure after oophorectomy, others[31] interpose a course of androgens. In support of the former, recent work[32] has suggested the greater effectiveness of adrenalectomy over androgens in patients with visceral metastases, and the fact that patients with visceral involvement succumb rapidly when they fail to respond to therapy. Aside from this situation, however, patients with soft tissue and skeletal metastases respond better to a major ablation than do those with visceral metastases. Whether to do ablation in the presence of cerebral metastases has not been specifically answered. Many feel that once unquestionable cerebral signs have developed such procedures are not worthwhile.

Androgens

With the era of experimental mammary tumorogenesis with estrogens just under way in the late 1930's, Loeser's idea that androgens might produce the "neutralization" of estrogens initiated the additive approach in hormonal palliation.[33] In spite of encouraging subjective and objective improvement in some cases,[34-36] it became clear that this was not going to be a stoicheometric relationship, and that even acceleration of the disease could occur. Urinary excretion studies suggesting conversion of injected androgens to estrogens in the body were offered to account for this, but could not be borne out by clinical correlation.[37,38] A premenopausal woman has a 20% chance of obtaining a remission, a postmenopausal 22%, with an increasing probability up to the ninth postmenopausal year where it levels off.[9] Androgens are used primarily when progressive disease becomes evident at a time when the tumor is still, presumably, sensitive to estrogenic stimulation, (i.e. when progression occurs within 5 years after a regression induced by an oophorectomy or major ablation, or within 5 years after a spontaneous menopause). After this latter 5 year period there is little statistical difference between the overall effectiveness of androgens and estrogens, although androgens are preferred in cases with predominantly ltyic osseous lesions.

Estrogens

Several investigators have long cautioned against the use of estrogens in thepremenopausal woman.[5,39,40] This opinion was reinforced by the results of animal experiments of Lacassagne and others,[41] but has never been confirmed by a large clinical study. Nevertheless, it has become apparent from smaller studies that the response to estrogen does have a relationship to menopausal age, and that the menstruant rarely shows regression, most frequently has no response, and occasionally demonstrates acceleration of her disease.[42-44] Recent work with massive doses of estrogen has shown but a transient regression in a few.[45] With the chance of obtaining a higher regression rate using other measures, estrogens have little place in the palliation of the premenopausal patient. After the menopause 37% will shown an objective regression, 12.5% being in the first 4 years and 38% being 4 or more year postmenopausal at which time a plateau of effectiveness is reached.[9] Soft tissue, nodular lung, and mixed or blastic osseous metastases are more likely to respond favorably to estrogens than androgens.

Progestational Agents

By itself the use of progesterone has not proven effective.[46] Recently, Huggins[47] was able to completely extinguish carcinogen induced mammary cancer in Sprague-Dawley rats by using a combination of estradiol benzoate and progesterone. As with so many promising animal trials, however, the transfer to the human situation has been disappointing.[48]

General Considerations

If the status and responsiveness of the disease is such that ablative and additive therapy can be offered, the accepted procedure is to employ one method at a time in sequence. Unless the disease is progressing rapidly, at least 3 months should elapse after initiating therapy before judging its efficacy. If hormones are being used they are given continuously during this period. Therapy should not be stopped and a new one begun until definite progression of disease is manifest.[9,42] In some cases when relapse occurs on either androgen or estrogen therapy, a change to the opposite hormone may produce another remission. Withdrawal of all hormonal therapy during a period of reactivation may sometimes be followed by a remission ("rebound regression").

There are several natural occurring and synthetic androgens and estrogens available[49,50] that can be used with equal effectiveness—the effectiveness being more related to their physiologic properties than any specific chemical configuration. Dosages have been determined using stilbestrol 15 mg. a day orally, and testosterone propionate 100 mg. three times a week, intramuscularly, as standards of reference. In the doses used all hormones masculinize or feminize, and may produce nausea and fluid retention.

CORTICOSTEROIDS

The theoretical assumption that one could affect a "medical adrenalectomy" through pituitary inhibition with large doses of corticosteroids has not been substantiated clinically. In fact, considering the actual variance of endocrine changes produced by a medical vs a surgical adrenalectomy, it is not surprising that some patients have had repressions with adrenalectomy after having had a progression while on corticosteroids.[30] Whatever the tumor regression described with the latter, it has been short lived and not comparable to what can be expected with a major ablation.[51] Studies supporting the augmentation of the disease with these compounds, as evident by autopsy findings of unusual gastrointestinal metastases and an overall decreased survival,[52] have not been generally accepted as a cause and effect. Nevertheless, corticosteroids have a definite place in the palliation program. To see a patient with cerebral metastases brought from unconsciousness to lucidity is an improvement which cannot be denied, and perhaps 75% of spontaneously occurring or hormone induced hypercalcemia can be reverted. Even if their only effect has been an increase in appetite and sense of well being it is felt that this is worthwhile.

The synthetic corticoids with minimal salt retaining properties are preferred. They are given in doses ranging up to the equivalent of 300 mg. of prednisone per day, as used in acute hypercalcemia, and all the side effects attendant with the use of "steroids" can be seen. Because of their low mineralocorticoid effect, however, they should not be used for adrenal insufficiency.

RADIOTHERAPY

For isolated skin recurrences, as a prophylax is against pathologic fractures of weight bearing areas, and for painful areas of skeletal involvement, radiation therapy has proved invaluable. Since about 40% of bone must be replaced by tumor before a defect can be detected radiologically, pain may precede objective evidence by 2 to 3 months. In any woman with breast cancer who has persistent pain referable to the skeletal system with negative x-rays and other causes of pain excluded, it is worthwhile giving a course of therapy empirically. The little space alloted this mode of therapy is because its general usefulness is undoubted.

CHEMOTHERAPY

Although chemotherapeutic agents must take a secondary place to hormonal therapy when considering their contribution to the total performance status of the patient, some, nevertheless, have proven very useful in certain areas of palliation. Perhaps the most significant contributions have been the relief of dyspnea by intravenous alkylating agents—especially when the dyspnea is on the basis of lymphangitic involvement. The other is the control of pain from skeletal metastases with the fluorinated pyrimidines. Both of these agents have produced transient regressions of soft tissue lesions. Objectively, their effect on skeletal and visceral metastases has not been encouraging.

OTHER MODES OF THERAPY

Confronted with a long terminal disability, in many cases, where livable days are at a premium, most have found it very rewarding to use more aggressive measures when dealing with local problems. For example, at least 25% of patients during the course of their disease will develop a recurrent, symptomatic pleural effusion. Repeated thoracenteses soon deplete plasma proteins. Intracavitary alkylating agents and radioactive elements have met with some success.[53] More complete and longer lasting results, however, appear to follow a pleural stripping of the involved side and a series is now being evaluated at this hospital. Whenever feasible, impending fractures in weight bearing areas should be pinned because once these patients become bedridden and inactive hypercalcemia poses a constant threat.

There remains one form of palliation to consider and it is the only one which must begin even before the initial mastectomy—that is, emotional. Little should have to be said in this era of the re-emphasized "total patient concept," but it is in the field of cancer where all too often the art of medicine has become so abstract it is unrecognizable. With the help of mass media the concept of cancer for the public has changed from the pathologic to the prognostic, and it places the physician in the extremely uncomfortable position of having the patient know as much about the course of the disease as he does. How simple becomes the sputter and pat on the back, rather than the long needed minutes of explanation, encouragement, and support.

PERSPECTIVE

Over 2000 years ago Celsus stated, "Only the beginnings of a cancer permit a cure." Because its location is more accessible to early discovery than many malignancies we have come to realize that the cure of breast cancer lies beyond the palpable, for no matter how small the lesion at discovery or how negative the nodes at surgery—the patient eventually dies of her disease. Conventional theory has made cancer a disease of cells with its beginning in one cell or a group of cells that have been fired off by some cause and then continue to grow wildly and relentlessly. It is the consideration of the hormone "dependence" of some tumors, however, along with the multicentric origins, age incidences, geographical variations and the spontaneous regressions of other tumors that have led some investigators to attack this approach. They point out[54] that "cellular behavior is still a reaction between the cell and its environment and cannot be reduced to mere terms of intra-cellular initiative alone." A plea has been made for a new emphasis on organismal organization in the field of neoplasia.

Wherever these beginnings will be found, at present, for the individual patient months and perhaps years of a more useful, symptom-controlled life can be offered by the use of one or more of the measures described.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Current Concepts in Surgery for Gastroduodenal Disease of the Aged. F. A. dePeyster and R. K. Gilchrist, *Surgical Clinics of North America, Vol. 43, Feb., 1963.*

This article deals with the changing concepts of surgical treatment for gastroduodenal disease of the aged (70 years and over) over a seventeen year period. The results showed: (1) that elective gastroduodenal surgery for benign disease is well tolerated by the aged (mortality 4.3%) in contrast to elective surgery for malignancy (mortality 25%) and, (2) that emergency operations whether for cancer or benign disease continue to carry four to five times greater mortality than the corresponding elective surgery. The greatest progress in the management of these aged patients has occurred in the field of supportive care including gastric cooling, repeated plasma infusions during the immediate post-operative period to combat hemoconcentrations, low renal output and poorly functioning anastomosis. Other advances have been in the use of serotonin antagonists to relieve the dumping syndrome, the use of newer mucolytic agents (N-acetyl-cysteine) and gamma globulin to reduce the incidence of serum hepatitis.

Histologic and Clinical Evidence of Post-Streptococcal Glomerulonephritis in Patients with the Nephrotic Syndrome. J. R. Lawrence, V. E. Pollak, C. L. Pirani, and R. M. Kark, *Medicine, Vol. 42, No. 1, pp. 1-24, January, 1963.*

Examination of renal biopsies from 15 patients with acute hemorrhagic glomerulonephritis revealed a histopathologic pattern characteristic of post-streptococcal glomerulonephritis. The typical pattern of endothelial and axial cell proliferation and accumulation of fibrillar PAS-positive material, without true membranous change, tended to persist after the acute exudative lesions had healed.

Renal biopsies from 84 adult cases of the nephrotic syndrome were then examined in an effort to distinguish those patients who had developed the nephrotic syndrome as a result of post-streptococcal glomerulonephritis. Cases of diabetes mellitus and systemic lupus erythematosus were excluded. In nine of 84 patients, the renal lesion was considered to be due to post-streptococcal glomerulonephritis. The histologic changes were equivocal in 13 cases. When a semiquantitative assessment of the histologic features was compared with an independent assessment of the likelihood of streptococcal disease from the clinical data, there was an excellent correlation. Post-streptococcal glomerulonephritis appears to be a relatively uncommon cause of the nephrotic syndrome.

Reconstruction of the Thoracic Esophagus by Means of a Right Colon Transplant. R. A. Tarizzo, A. Gabel, E. W. Staub, and S. G. Economou. *Surgical Clinics of North America, 43: pp. 11-30, Feb., 1963.*

The diseased esophagus has been replaced by skin tubes, inert prostheses, gastric tubes, preserved aorta, jejunum, and colon. In this paper the authors describe the management and technique of right colon transplant.

Pre-operative management includes a careful general medical evaluation, esophagoscopy, bronchoscopy, barium swallow and enema, supplementary high-protein feedings and vitamins, with or without gastrostomy, if nutritional status is inadequate, and, just prior to surgery, liquid diet, mild cathartics and non-absorbable antibiotics per os. The operative technique of right colon transplant is described in detail with numerous illustrations. The right and transverse colon is mobilized, and the ileocolic vessels divided after temporary occlusion has demonstrated satisfactory viability. The colon segment is rotated and passed through a retrosternal or subcutaneous tunnel to the neck, where the cecum is anastomosed to the cervical esophagus or hypopharanx. Cologastrostomy and ileotransverse colostomy conclude the transplant procedure. Gastrostomy is advised, and, if vagotomy is done, either because of prior or simultaneous esophagectomy or high gastric acidity, pyloroplasty is indicated to provide satisfactory gastric drainage. Postoperative management includes inspection of the cervical anastomosis at two or three days, Gastrografin swallow at a week, and, if both are satisfactory, progressive diet may be begun.

This procedure has been done in patients with esophageal cancer, esophageal stricture, and acquired bronchoesophageal fistula. Three representative case histories are presented.

DNA Synthesis as a Marker in Fractionated Radiation Therapy. F. R. HENDRICKSON and H. H. SKY-PECK. *Radiology, 80:2 p. 244, Feb., 1963.*

Exposure to ionizing radiations produces a marked suppression of DNA synthesis by mouse tumor. This is predominantly due to a decrease in the number of cells in the synthesis phase and to some extent a decrease in synthesis rate. This suppression lasts several days and is followed by a recovery and rebound on the 3rd to 5th day. This recovery time is independent of dose. Human tumors show a similar cyclic change after irradiation. Intestinal mucosa follows a similar suppression-recovery rebound pattern but with a shorter interval. The possibility of increasing effect by synchronizing subsequent radiation exposures with the rebound phase is suggested.

Head Injuries in the Emergency Room. ERIC OLDBERG. *Chicago Medicine, 66:2, Jan. 26, 1963.*

First ascertain the patient's general condition and the possibility of the presence of injuries elsewhere than to the head. In the order of importance with regard head injuries the neurological examination should consist of: 1) an evaluation of the patient's state of consciousness 2) observe whether or not the patient moves all four extremities 3) examine the pupils as to equality 4) the toe signs are extremely important because pathological toe signs indicate definite cerebral damage 5) note any leakage of blood and/or cerebrospinal fluid from the nose or ears. Charting should include blood pressure, respirations, pulse rate and quality, and rectal temperatures. Immediate X-rays of severe head injuries are rarely in order. As far as sedatives are concerned never use narcotics. The site of the blow to the head should be examined in order to determine whether the wound is open or closed, whether there is compounding of the bone fracture, whether lacerated brain is extruding, and whether or not there is depression. If a compound fracture of the skull has been produced the patient should be put on antibiotics. The debridement of the wound should be an operating room procedure. This is also true of penetrating wounds. If the scalp is hemorrhaging severely stop it with a pressure dressing.

The Effect of 5-Iodo-2-Desoxyuridine (IDU) on Virus and Cell Multiplication. A. W. HOLMES, RICHARD C. EY, and FRIEDRICH DEINHARDT, *J. Lab. & Clin. Med. 60:5,885, Nov., 62.*

Studies conducted on patients with herpes simplex keratitis revealed that although IDU has some beneficial effect on the disease it is not superior to current modes of treatment. Serial virus assay of infected rabbits treated with this agent showed no lasting benefit and indeed it appeared that the immune status of the animal was of more importance in determining the outcome of the illness than was IDU treatment. **In vitro** studies in cell culture showed suppression of virus synthesis only when cellular multiplication was also suppressed. IDU has no effect on extracellular herpes simplex virus.

Cholelithiasis in an Eight-Year-Old Child with Sickle Cell Anemia. *Case Report and Review.* E. A. Dainko, A. F. Bowyer, F. R. Johnson and E. J. Beattie. *AMA Arch. Surg., 86:203-209, February, 1963.*

The case of an eight-year old child with sickle cell anemia and gallstones is reported. A review of the literature in included. Seven cases of cholelithiasis in children with sickle cell anemia under the age of fifteen years were reported prior to that of the authors'. Cholelithiasis is found more frequently today in the child than is cholecystitis. Hemolytic disease is the most common cause of gallstones in children. Other factors in the etiology of gallstones are included in the discussion. The picture of gall-bladder disease in the child is not usually similar to that in the adult. Frequently they are asymptomatic and therefore may be present for years before diagnosis. The significance of jaundice in patients with gallstones and sickle cell anemia is discussed. Some pathophysiology in sickle cell anemia is briefly mentioned. Abdominal pain is common in children with sickle cell anemia and in evaluating a patient with sickle cell anemia in an abdominal crisis the diagnosis of gall bladder disease should be entertained and a cholecystogram should be done as part of the evaluation.

Equivocation as a Bedside Manner. (*Editorial*) E. F. Traut, *Chicago Medicine, 64:5, June 9, 1962.*

Some people, patients as well as doctors, are chronic equivocators. To the question, "How are you feeling today?" the patient may answer, "Not too well." Additional questioning is needed to elicit the history of sleeplessness or vomiting. Then there is the doctor apprising the pneumonia patient of the "little congestion in a lung," the tuberculosis patient of a "little spot," the cancer patient of a "few abnormal cells." It is classically expressed in the extreme by the sophistry of the medical student's "a touch of pregnancy."

Equivocation is the mechanism used by many in telling facts, presumably unacceptable or, at least acceptable with difficulty. Of all illnesses, malignant tumor conveys to the public the grimmest outlook. Here, equivocation or negation are frequently subterfuges for the naked truth. In such instances advisable procedures cannot be generally applied. "Always, never and must be" do not apply. The only rule is no rule—individualization. Circumstances can vary, from patients with noninvasive, completely controllable neoplasms to those with histologically proven, widely metastasized-apparently inevitable death. Obeying such common requests, as "Don't, under any circumstances, tell mother," can be loaded with danger. The patient can fail to make necessary economic moves and gestures dictated by sentiment as well. He is unprepared to accept with some equanimity pain-relieving but otherwise ineffective medical efforts.

Frankness, synonymous with honesty, need not be brutal nor even abrupt. The apologetic attitude of the physician may be interpreted by the patient as defensive with overtones of guilt. The doctor should not assume responsibility for the symptoms, the course, nor even for the outcome of the patient's illness.

Pre-Eclampsia and Eclampsia Early in Pregnancy. L. J. Schewitz, V. E. Pollak, C. L. Pirani and P. Stein. *Am. Journ. Obst. Gyn. 84:10 pp. 1330-1342, November 15, 1962.*

In a series of 77 patients with the toxemia syndrome studied by renal biopsy, pre-eclampsia occurred in 9 between the nineteenth and twenty-eighth weeks of pregnancy. Eight of the patients were 25 years of age or younger. Seven were primigravidas.

Lesions characteristic of pre-eclampsia were found in each initial renal biopsy. In all but 1 (taken 8 days after delivery) the lesions were graded as severe or moderately severe. In addition to these lesions, arteriolar sclerosis was noted in 5.

Serial studies were performed in 6 patients. Arteriolar nephrosclerosis, not observed in the first biopsy, was seen in the second biopsy of 2 (9 and 4½ months after delivery). The underlying arteriolar sclerosis had progressed in 2, and remained static in 1. In only 1 patient were there no residual renal vascular lesions. Elevated blood pressure levels persisted post partum in 3, and proteinuria persisted post partum in 2 others. Both had arteriolar nephrosclerosis although they were normotensive at the time, and both developed pre-eclampsia in subsequent pregnancies.

The 9 patients with pre-eclampsia early in pregnancy differed from those with pre-eclampsia after the twenty-eighth week in that (a) they all had clinically severe pre-eclampsia, (b) there was a high incidence of underlying renal vascular disease, and (c) there was a high rate of residual renal vascular damage.

Isolation of a new Herpes-like Virus from South American Marmosets. A. W. Holmes, Robert E. Dedmon, and Friedrich Deinhardt, *Federation Proceedings, April, 1963.*

In the course of an evaluation of the marmoset as a laboratory animal we have repeatedly isolated a virus which satisfies all the chemical and physical criteria for membership in the herpes virus group. It is pathogenic for marmosets, mice, rats and rabbits and produced liver and adrenal lesions similar to those seen in visceral herpes simplex infections. It is not neutralized by antisera to herpes simplex, herpes B, pseudorabies, and SA-8. It would appear, therefore, that this agent is a previously undescribed member of the herpes virus group.

Bifurcational Anastomosis of Small Arteries with Pedicled Graft. B. L. Lindstrom and Geza de Takats. *Surgery 53:3 p. 340, March, 1963.*

A pedicled graft was used to restore patency not only to the main channel, but to an important branch. The point of anastomosis was at the origin of the saphenous artery from the femoral.

Using magnifying lens, fixation and stay sutures and no anticoagulants, one-half of the saphenous arteries with an average external diameter of 1.4 millimeters remained open. This type of graft may be applicable at the level of the profunda femoris and at the origin of the sural and peroneal branches. An autogenous vein seems the most suitable material for the reconstruction of small arteries.

ABSTRACTS AND REVIEWS

Progress in the Diagnosis and Surgical Treatment of Insulin Secreting Tumors of the Pancreas. R. J. FREEARK and F. A. DEPEYSTER, *Surgical Clinics of North America, Vol. 43, Feb., 1963.*

Episodes of neurologic or psychotic manifestations due to insulin secreting tumors of the pancreas may provide difficult diagnostic problems leading to delay and permanent central nervous system damage of the affected patient. Such a clinical experience is cited. The differential diagnosis between functional hypoglycemia, early diabetes and organic hyperinsulinism may be difficult in the presence of borderline fasting blood sugar determinations. Here, the leucine and/or sodium tolbutamide tests are helpful, economical and may be performed as an out patient test. Surgical excision of the offending insulin secreting tumor is the treatment of choice except when the patient refuses surgery, or the risk is too great or, in the presence of far advanced metastatic disease, where steroids and dietary management are of value.

Mumps. FRIEDRICH DEINHARDT, M.D., *Medical Science (Lippincott's). Vol. 11, Number 10, May 25, 1962.*

This is a review article on the disease, complications, pathogenesis, virus, laboratory diagnosis, treatment, epidemiology and prevention of mumps. Recent work on the development of killed and attenuated virus vaccines are discussed in detail.

The Phenomenon of Leucine Sensitivity, by T. B. SCHWARTZ, E. BOWYER, and P. HANASHIRO, *The Medical Clinics of North America, January, 1963.*

The amino acid, L-leucine, provokes or accentuates hypoglycemia in circumstances in which real or potential hyperinsulinism exists. Its probable mode of action is two-fold: (1) the stimulation of "sensitized" beta cells with a resultant release of insulin and (2) an enhancement of some extrapancreatic mechanism, perhaps hepatic, affecting blood sugar regulation. The significance of the phenomenon of leucine sensitivity lies in the fact that the elucidation of its mechanism of action may furnish greater insight into the homeostatic control of the blood sugar.

The Adult Fanconi Syndrome, Report of Two Cases, One with Multiple Myeloma, by R. E. DEDMON, J. H. WEST and T. B. SCHWARTZ, *The Medical Clinics of North America, January, 1963.*

Two cases of the Fanconi syndrome in the adult are reported. One patient had renal tubular reabsorptive defects associated with osteomalacia, macroglobulinemia, multiple myeloma, a coagulation defect, and liver disease. The second patient had renal tubular defects associated with osteomalacia and chronic pyelonephritis.

The possible pathogenesis of the syndrome in these patients in relation to current biochemical and genetic concepts is discussed. The reasons for development of this particular syndrome in patients with such common disorders as myelomatosis and pyelonephritis remain an enigma.

Treatment consists of correction of the systemic acidosis, repletion of potassium when necessary, and the use of supplemental calcium, vitamin D and anabolic steroids.

A Time-Motion Study of Urinalysis. J. C. Ashton, A.R.T., and J. C. Lashof, M.D. *Can. J. Med. Tech., Feb., 1963.*

A time-motion study of the different steps involved in performing a routine urinalysis by several methods was undertaken. The amount of glucose present in the urine was determined by Benedict Solution, Clinistix, Clinitest and Combistix; the amount of protein by sulfosalicylic acid, Albustix and Combistix; pH by Phenyl Nitrazine Paper, Litmus Paper and Combistix and ketones by Rothera's Method, Ferric Chloride and Ketostix. A complete urinalysis was done by four different combinations of the above tests, the method for specific gravity, colour, clarity and microscopic remaining constant for all four combinations. Times were determined for: 1. the various tests performed individually, 2. a single complete routine urinalysis and 3. routine urinalysis done in a series of twenty. The data is analyzed as to the percentage of time saved by the use of Combistix as compared to the usual standard method, and the significance of this time-saving in relation to a complete urinalysis including data on pick-up and delivery of results.

The use of Combistix for pH, glucose and protein has been shown to result in a significant reduction in time required both for a single urinalysis and in a series of 20.

Spontaneous Rupture of the Stomach. C. Davis, R. Andresen, O. Akre and W. McCarthy, *Archives of Surgery, Vol. 86, No. 1, January, 1963.*

An unsuspected case of spontaneous rupture of the stomach is reported in an adult. Recovery followed early surgical intervention and successful closure of a longitudinal perforation in the anterior wall of the stomach.

Factors are discussed concerning the possible pathogenesis of spontaneous rupture of the stomach.

Although spontaneous rupture of the healthy stomach is of infrequent occurrence, this condition should be considered in the differential diagnosis of acute surgical lesions of the abdomen. Early roentgen examination of the abdomen will aid in making the diagnosis.

Recorded cases indicated that spontaneous rupture of the stomach has been found more frequently at autopsy than at operation. Early recognition and prompt surgical treatment of a spontaneous rupture of the stomach will result in an increased incidence of survivals.

Chemotherapy of Human Cancer with Sulfhydryl Inhibitors. F. E. Knock, *Archives of Surgery, Vol. 86, No. 3, March, 1963.*

In agar plate assays with living human cancer cells from 40 of 40 consecutive surgical specimens, one or more sulfhydryl inhibitors, alone or with adjuncts, has exceeded the activity of drugs commonly used for cancer palliation, such as HN_2 or methotrexate. Seven patients with far-advanced cancer whose tumors could be followed objectively have been treated with sulfhydryl inhibitor oxophenarsine (Mapharsen) plus chemical adjuncts fluoride, malonate and heparin, and in some cases varying forms of radiation-potentiating chemotherapy: diathermy, microwave, and ultrasound. Good regressions have occurred in four patients. Results to date indicate promise of the chemotherapy, but more data are needed for full evaluation. Clinically the chemotherapy in selected cases is being combined with cryogenic congelation of large masses of cancer and administration of autogenous vaccines.

Induction of Resistance to Sarcoma 180 Tumor in Mice. T. J. McNair, E. Hoppe and W. H. Cole, *Archives of Surgery, Vol. 86, No. 2, February, 1963.*

We have compared the effect of incubation of 440,000 Sarcoma 180 cells for 24 hours in guinea pig serum, and a similar number of cells incubated in rabbit serum on growth of the cells. Each mixture was inoculated every other day for 3 injections, subcutaneously into Swiss mice. Takes were sustained in 20% of 30 mice receiving the 3 injections of cells and rabbit serum, compared to 100% of 30 mice injected with cells and guinea pig serum. When these animals receiving the 3 injections of attenuated cells were challenged with fresh Sarcoma 180 cells, the takes were much lower than in the control animals receiving fresh cells only, but complicating factors (e.g., take or no take following injection of attenuated cells) makes interpretations difficult.

The Treatment of Malignant Pleural Effusions by Partial Pleurectomy. E. J. Beattie, Jr., *The Surgical Clinics of North America, Vol. 43, No. 1, February, 1963.*

The diagnosis and modes of therapy for malignant pleural effusion have been discussed.

A thoracotomy with partial pleurectomy is recommended in those patients who seem able to tolerate surgical intervention.

Effusion has never recurred postoperatively. The prognosis is dependent on the status and control of the tumor involved.

Marital Disharmony: Concurrent Therapy of Husband and Wife by the Same Psychiatrist. An Analysis of the Therapeutic Elements and Action. A. P. Solomon, and B. L. Greene, XXIV, *Diseases of the Nervous System, 1:21-28, January, 1963.*

The authors analyze the therapeutic elements and action of concurrent therapy of husband and wife by the same therapist and describe the derivation of their technique and give the indications and contraindications. The acceptance of a couple for concurrent therapy at a time when they are under great stress is reacted to by them with feelings that they are getting emotional support. In the presence of hope and powerful positive social and cultural influences for the maintenance of the marriage state, husband and wife cooperate more readily for the purpose of making a workable marriage and become stimulated to examine the frustrations of the unconscious unattainable hopes that led to their marriage crisis, and to substitute for these new attainable goals and hopes. Hope was regarded as an integrated force in the therapy.

Another very significant therapeutic element in concurrent therapy is the changing multi-dimensional view of the marriage interactions gained by the psychiatrist from the communications given by the spouses from a frame of reference of often contradictory appraisals of each others attitudes, and from reports of their family life. These feelings and reports are communicated explicitly and implicitly in their behavior, in their account of situations involving the other, in their description of their attitudes toward one another, in their dreams, and in their transference transactions. Thus through this triadic communication system knowledge is gained in a minimum of time of both the nuclear and extended family transactions, and of the immediate and peripheral environmental situations and influences.

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RADIOGRAPHY IN RENOVASCULAR HYPERTENSION

Richard E. Buenger, M.D.

The radiographic examination of the urinary tract provides excellent visualization of the morphologic and functional changes occurring as a result of vascular lesions which produce hypertension. Paradoxically many patients with such serious lesions are found to have "normal" excretory urograms. We feel that meticulous care in performing the examination and a diligent study of the radiographs will identify, localize and delineate most of the lesions capable of producing a surgically curable hypertension.

EXCRETORY UROGRAPHY

It must first be understood that the urogram is only part of the battery of tests to be performed in the search of a surgically curable renal artery disease. Because of safety and simplicity, it is often one of the first tests to be performed. The patient should report to the radiologist in a dehydrated state, with a thoroughly cleansed intestinal tract.

After inspection of the plain film of the renal area for abnormal calcifications, the iodinated contrast material is injected intravenously as rapidly as possible, followed by serial radiography of

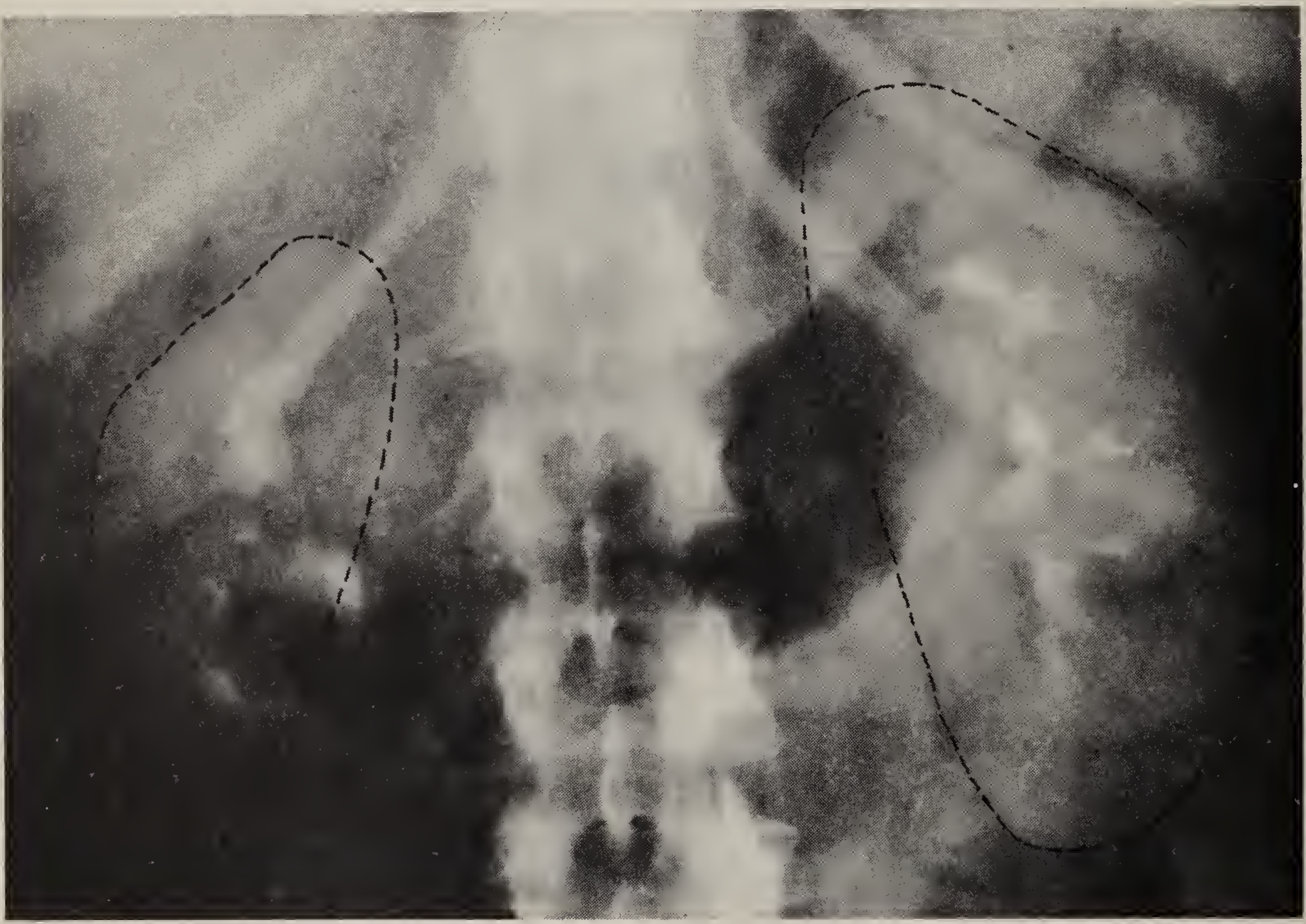

Fig. 1.— Excretory urogram. Decreased renal size on the right is the only noticeable abnormality. (Fibromuscular stenosis of right renal artery.)

From the Division of Radiology & Nuclear Medicine

the kidneys at 30 seconds, and at 1, 2, 3, 5 and 15 minutes. Oblique, upright, prone, delayed or compression radiographs are obtained as indicated to exclude inflammatory, obstructive or mass lesions.

The typical findings in the unilateral ischemic kidney which is producing hypertension are: A. Decreased renal size. (Fig. 1), B. Delayed nephrogram. (Fig. 2), C. Late appearance of calyceal and pelvic filling without dilatation of collecting system. (Fig. 3), D. Hyperconcentration of contrast material (due to increased tubular resorption of water) in affected kidney. (Fig. 4), E. Compensatory increased volume of collecting system on opposite side. (Fig. 5), F. "Notching" of the pelvis or ureter. (Due to collateral arterial blood supply around the stenotic area). (Fig. 6), G. Elongation of infundibula and clubbing of calyces. (Localized in infarct—generalized in ischemia.) (Fig. 7).

The patient is then hydrated, either rapidly with intravenous saline solution (with or without diuretic) or slowly by oral fluids. In the first instance, serial radiographs will show a *decrease* in the pyelographic density of the *normal* kidney, while the ischemic kidney *remains* more dense because it has a relatively increased resorption of water. With slow hydration (24 hours), a reinjection of contrast material must be made thé following day.

RENAL ARTERIOGRAPHY

When the excretory urogram, radioactive 1^{131} hippuran renogram, differential renal function studies, or a strongly positive history and bruit over the abdomen suggest unilateral renal artery disease, the morphologic changes responsible may be demonstrated arteriographically.

The renal arteries may be filled with contrast material by large rapid intravenous injections, translumbar puncture of the aorta, left transbrachial pressure injection or catheterization of the aorta and renal arteries via a femoral artery. The technique employed must be varied

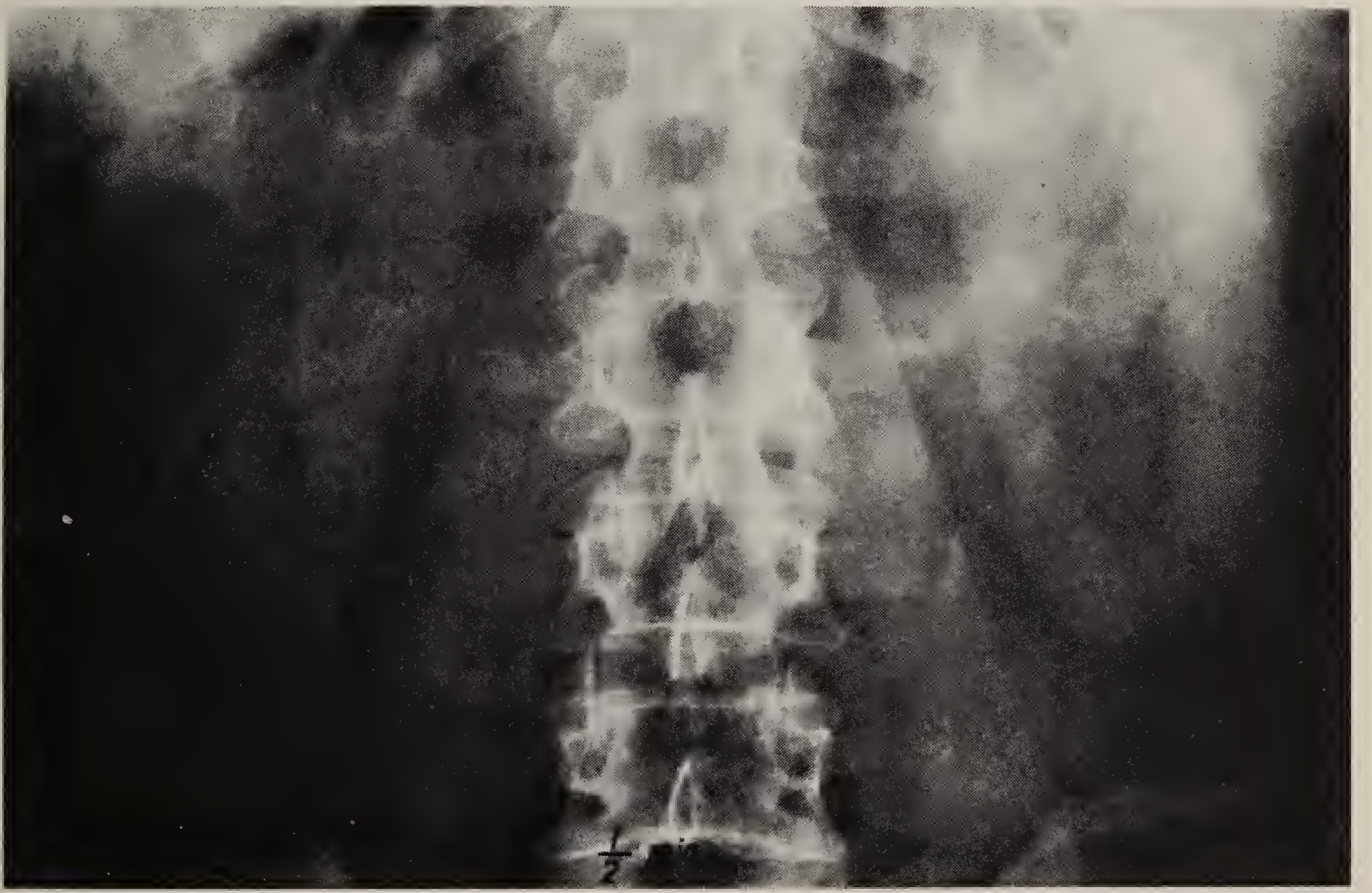

Fig. 2.—Marked decrease in nephrographic effect (90 seconds after rapid intravenous injection of contrast material) in ischemic right kidney. (Atheromatous stenosis of right renal artery.)

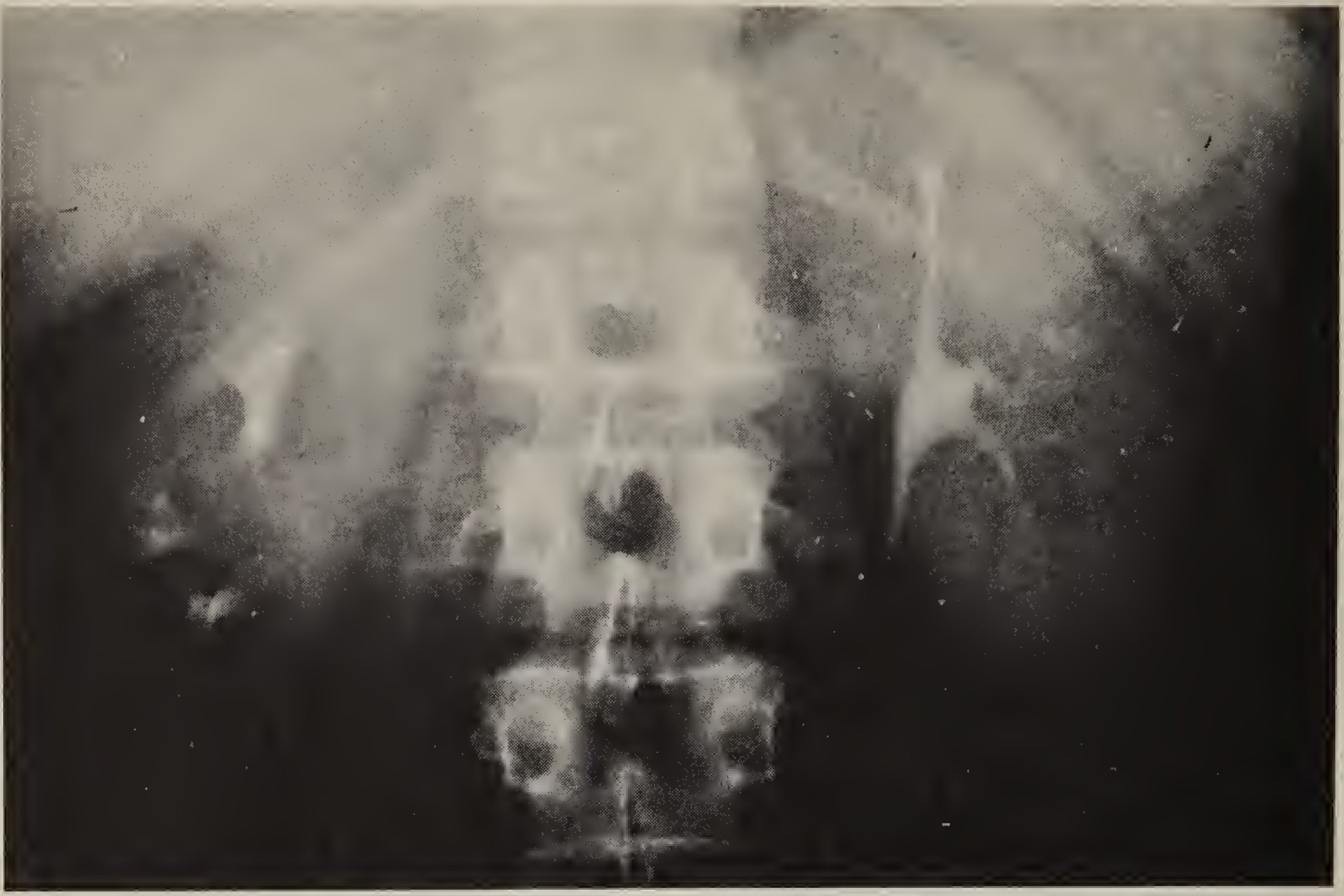

Fig. 3.—Delay in appearance of pyelogram in right kidney without dilatation of collecting system. (Fibromuscular stenosis of right renal artery.)

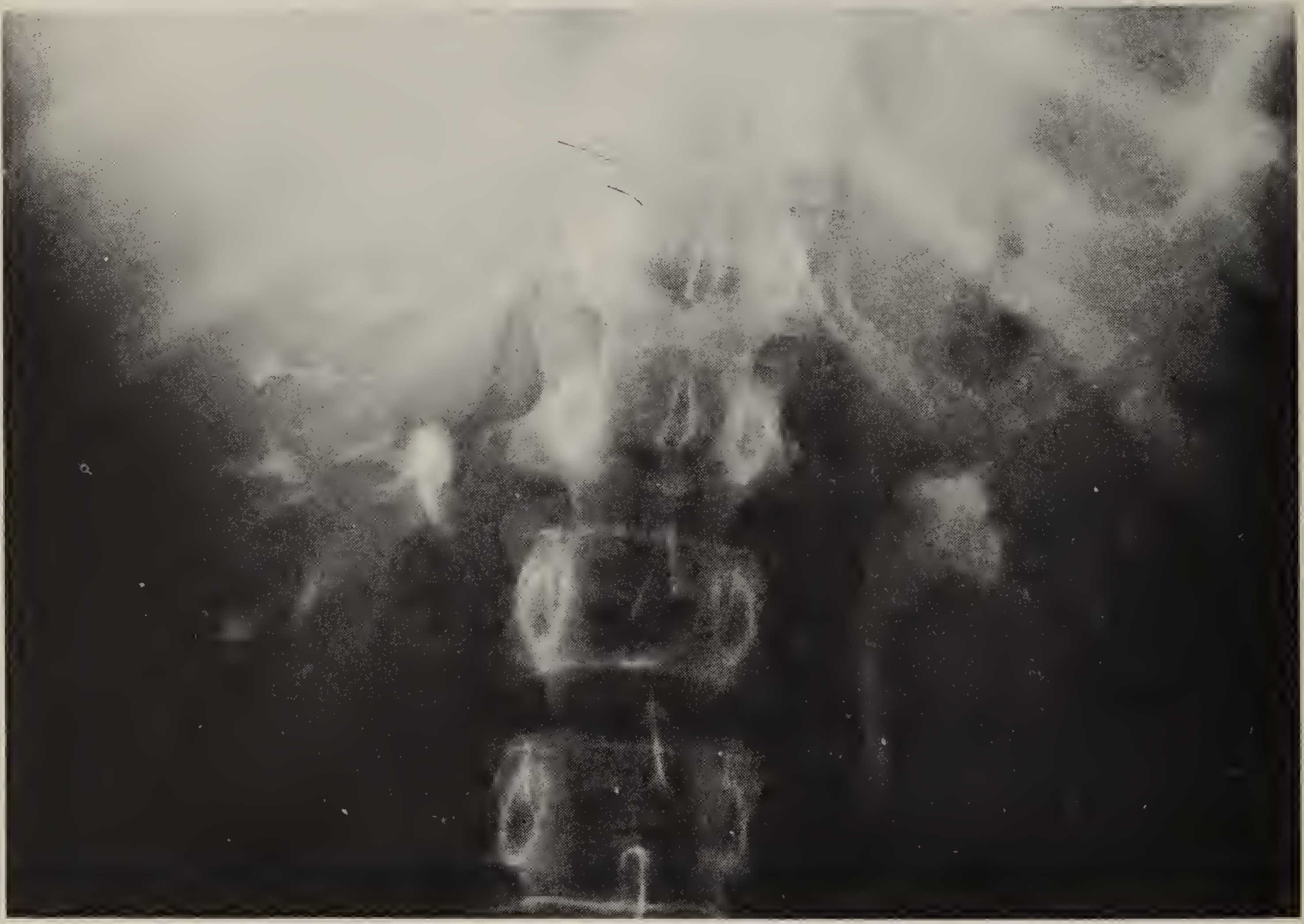

Fig. 4.—Decreased volume and hyperconcentration of contrast material on right. (Fibromuscular stenosis right renal artery. Fig. 10 is arteriogram of this patient.)

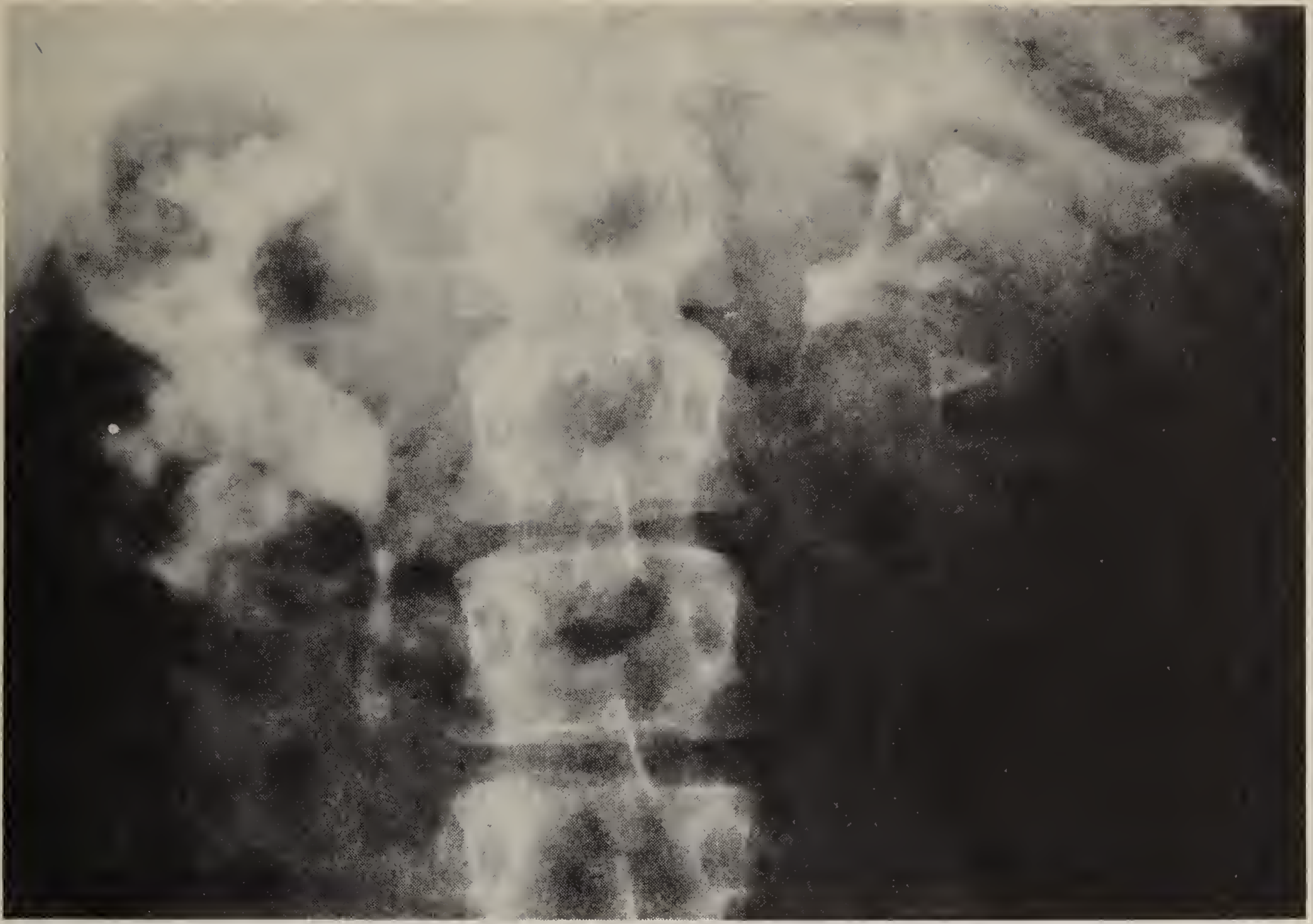

Fig. 5.—Small kidney, decreased volume of pelvis and notching of pelvis and ureter on left due to collateral arteries. (Fibromuscular stenosis of left renal artery.)

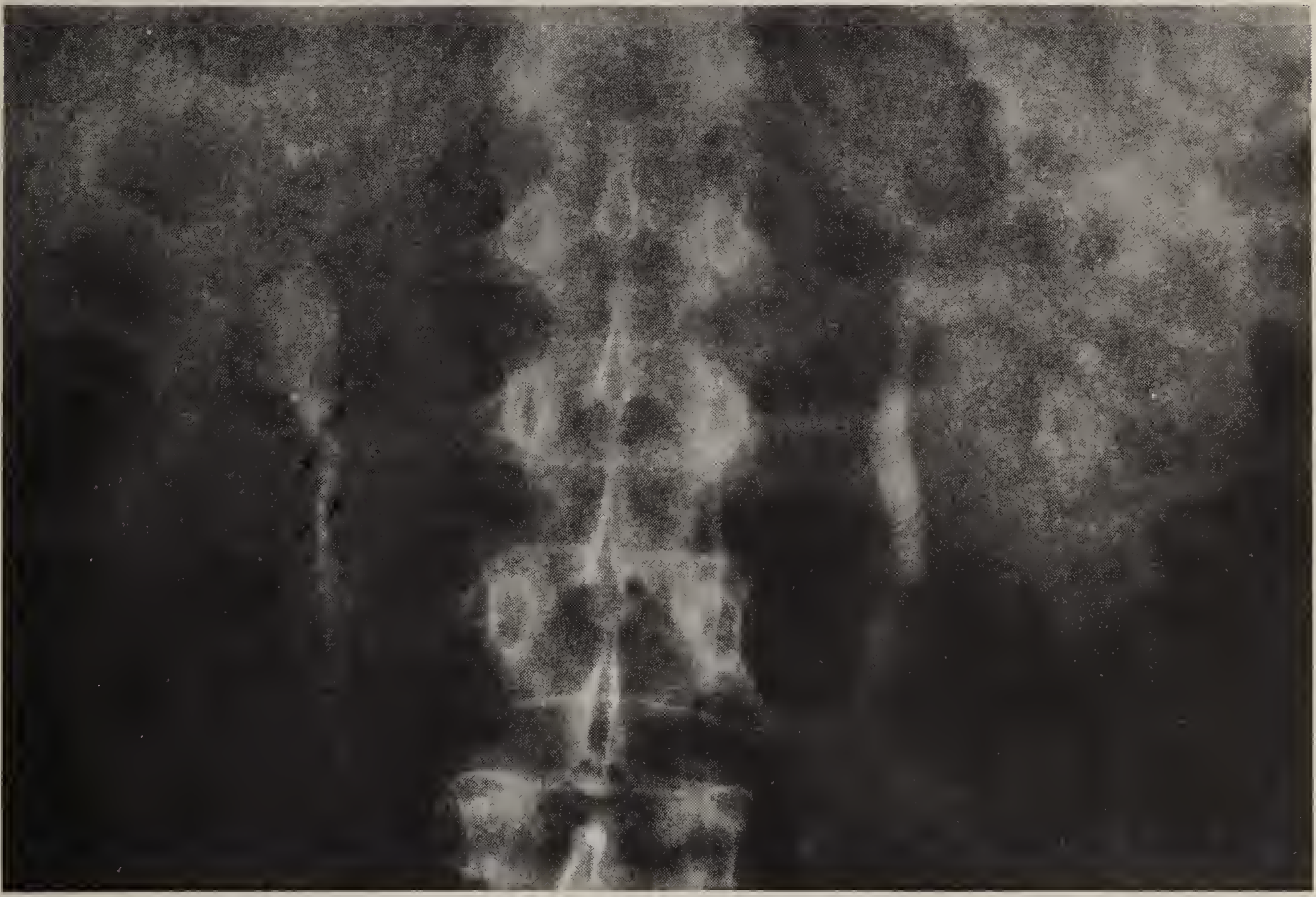

Fig. 6.—Marked notching of right ureter (ARROWS) due to collateral ureteral arteries. (Complete stenosis of right renal artery due to fibromuscular hyperplasia. Same patient as Fig. 8.)

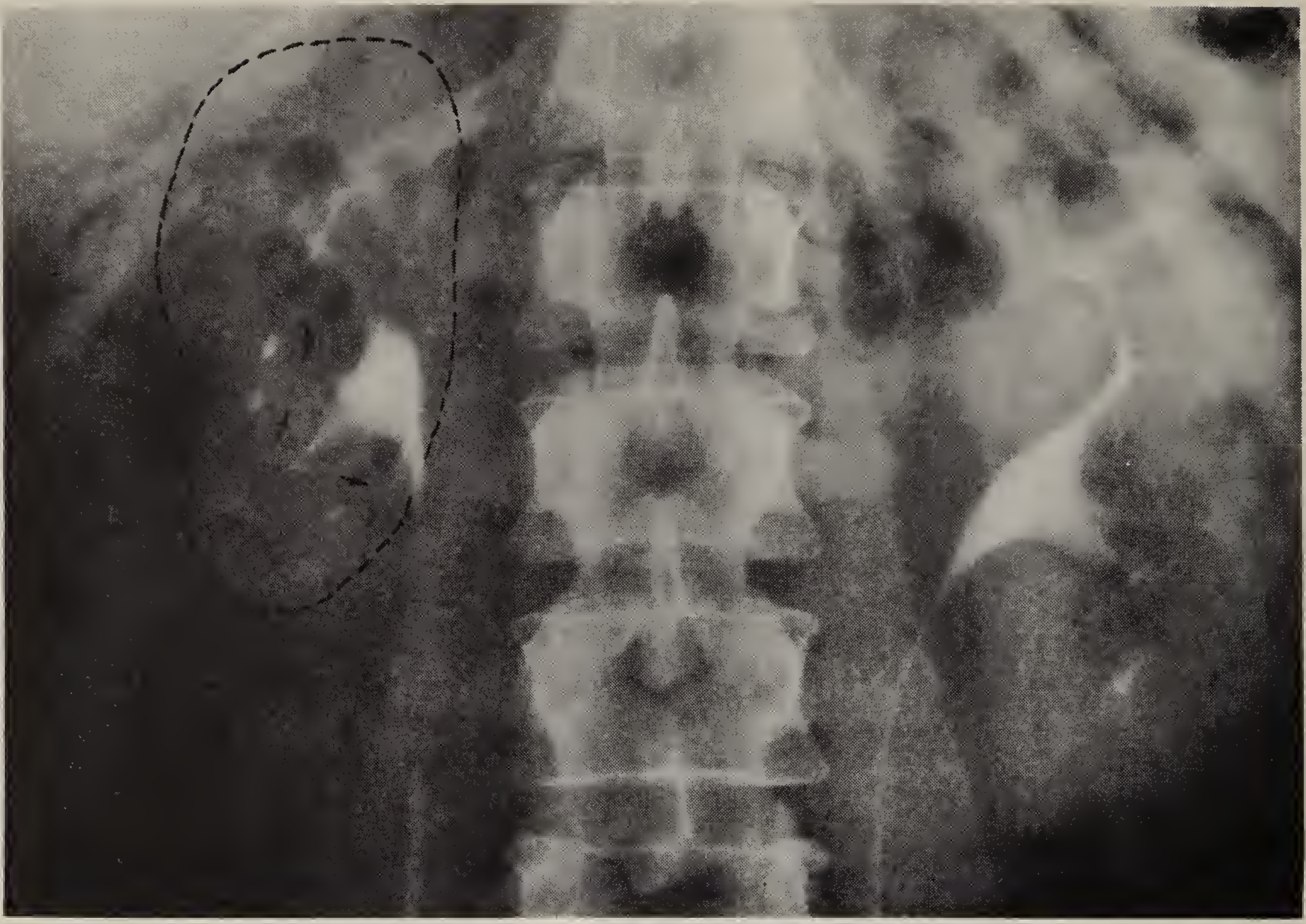

Fig. 7.—Notching and atrophy of renal cortex at right lower pole and elongation of calyceal infundibula locally on the right. (ARROWS) (Atheromatous stenosis of branch of right renal artery.)

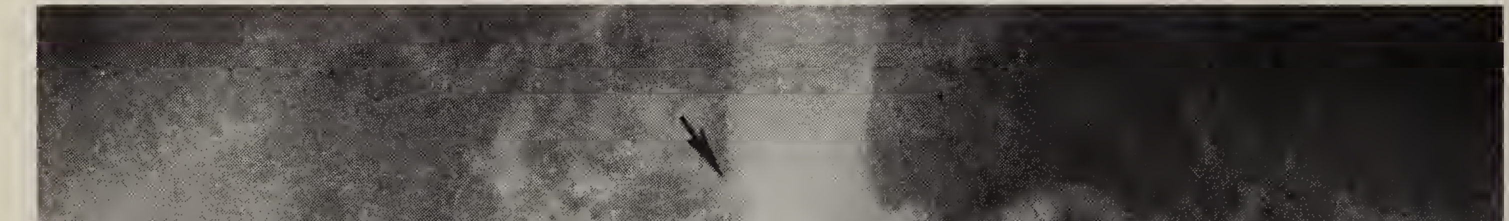

Fig. 8.—Complete obstruction of right renal artery (ARROW) with marked collateral bed in tissues surrounding the kidney. (Same patient as Fig. 6.)

by the skill and preference of the operator and the associated vascular disease present. Whatever method is used, it is imperative that dense opacification without overlapping vessels be obtained in several different projections. This can be achieved most often with the femoral catheter. If serial exposures are made, the opacification of the renal parenchyma vividly follows the arteriogram.

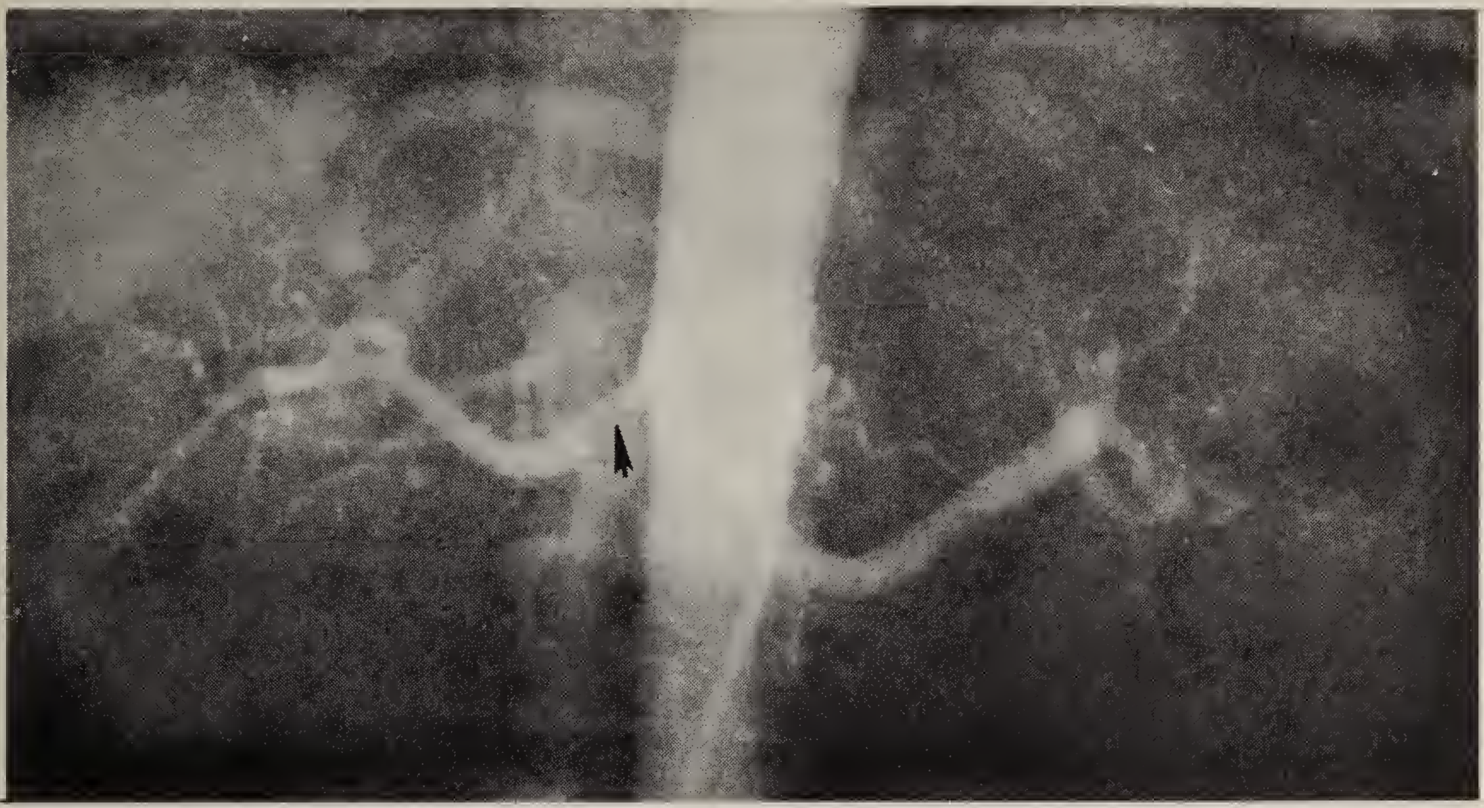

Fig. 9.—Atherosclerotic plaque of proximal renal artery (ARROW) without post-stenotic dilatation. Not believed to be producing hypertension.

Fig. 10.—Marked fibromuscular narrowing (ARROW) of right renal artery with post-stenotic dilatation. (Same patient as Fig. 4.)

Typical arteriographic findings will be: A. Non-filling of renal artery. (Fig. 8). B. Atherosclerotic narrowing of artery. (Fig. 9), C. Fibromuscular stricture (Fig, 10) or bands (Fig. 11) in the main renal artery or a branch. (Fig. 12), D. Post-stenotic dilatation of the artery. (Fig. 13), E. Collateral vessels filling the distal artery. (Fig. 14), F. Wedging or notching of the renal cortex during the nephrographic phase due to infarction or ischemia.

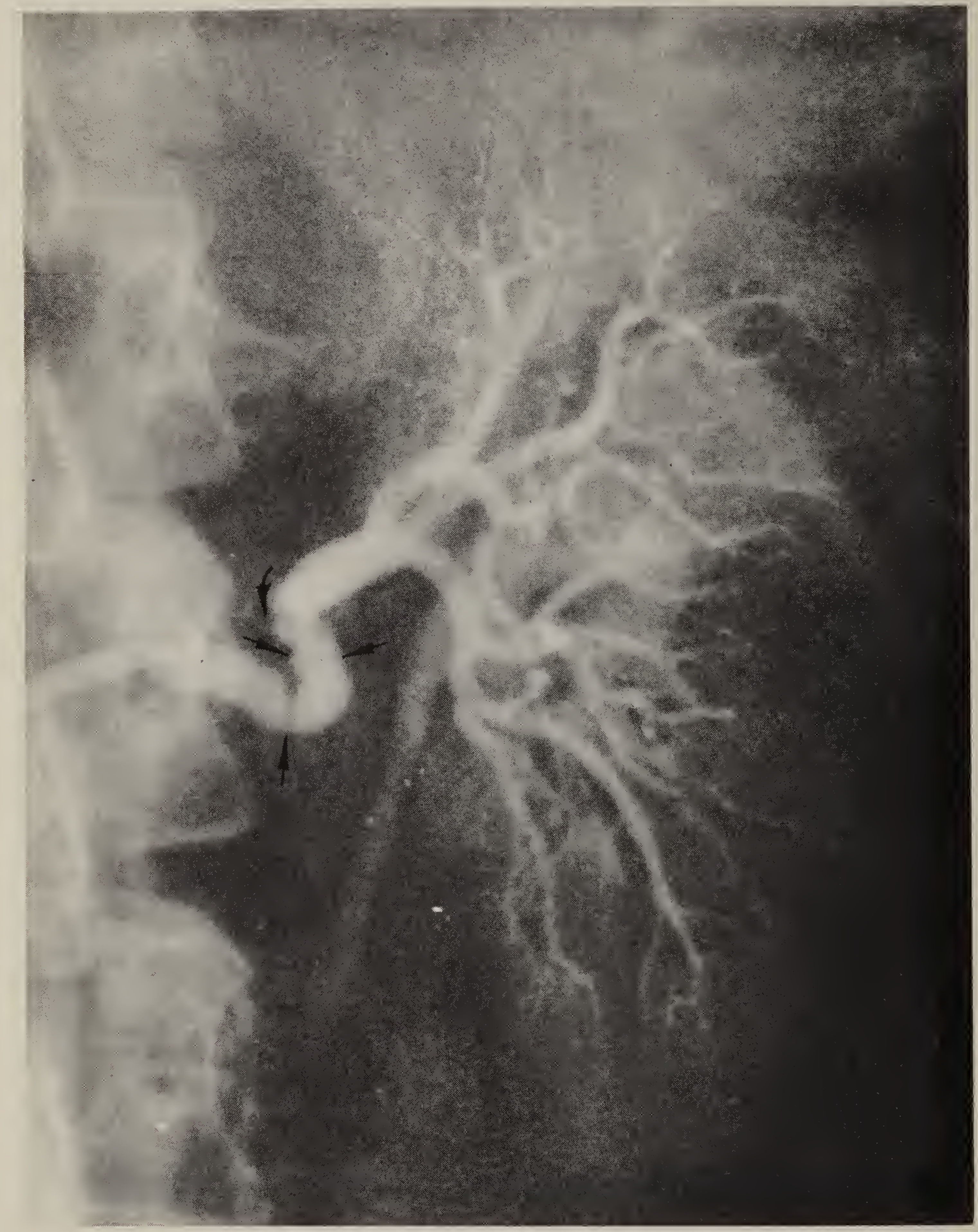

Fig. 11.—Multiple fibromuscular bands (ARROWS) in left renal artery. Marked decrease in arterial pressure across this area.

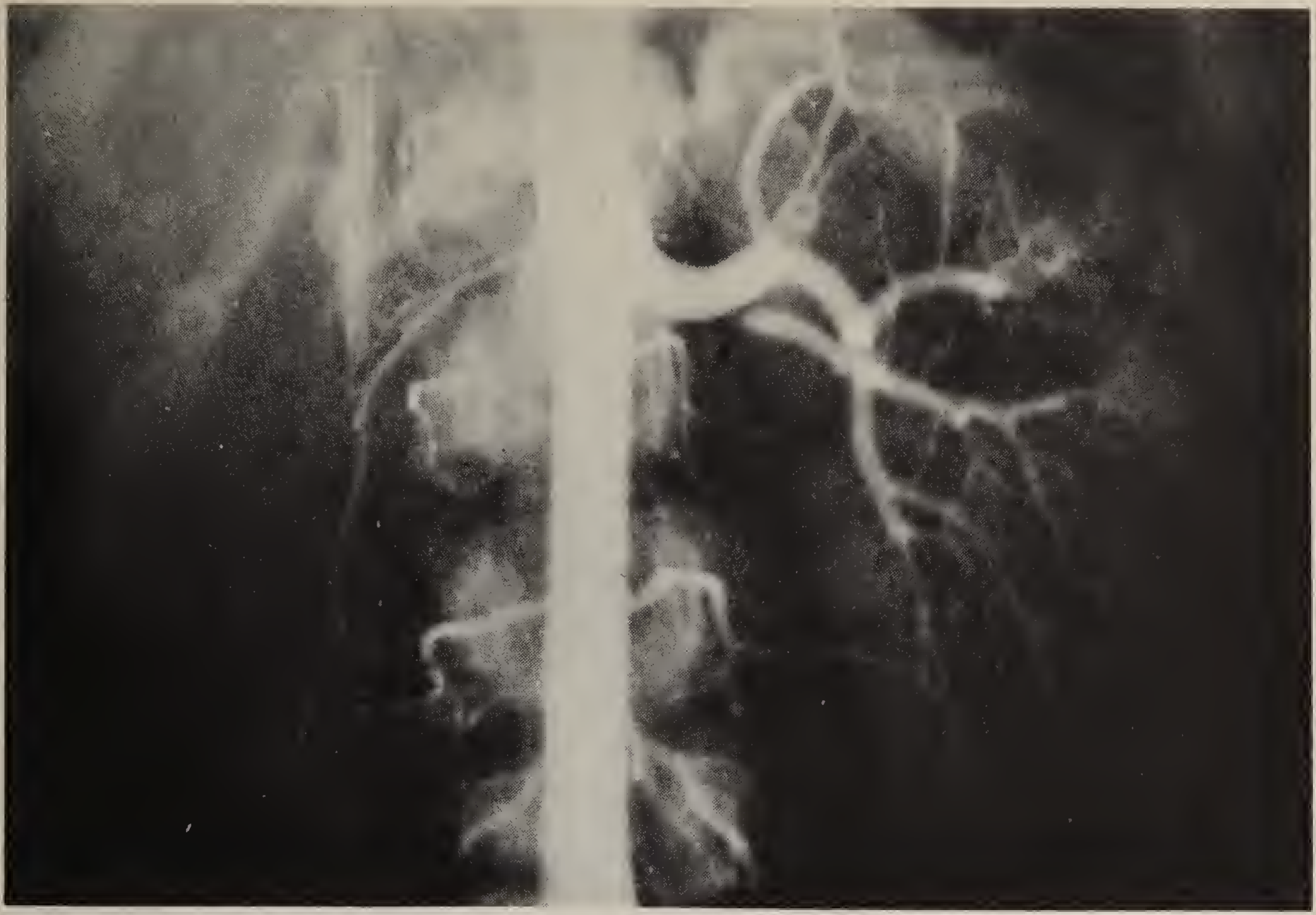

Fig. 12.—Stricture (ARROW) of *branch* of artery to congenital unilateral kidney.

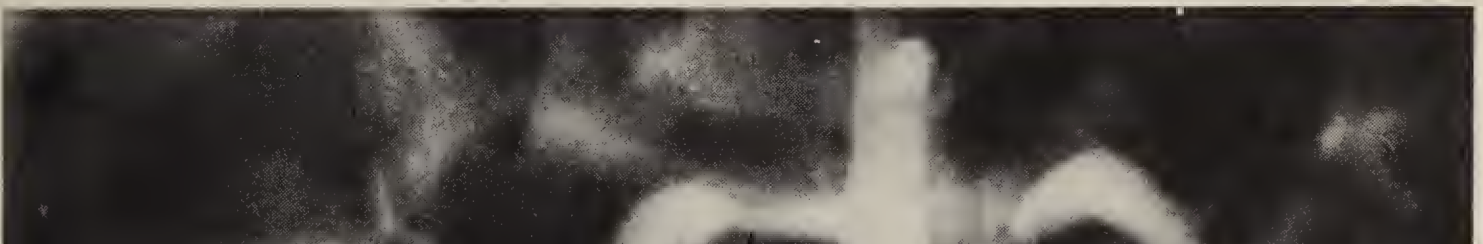

Fig. 13.—Bilateral fibromuscular strictures (ARROWS) of renal arteries with marked post-stenotic dilatation in 5 year old hypertensive girl.

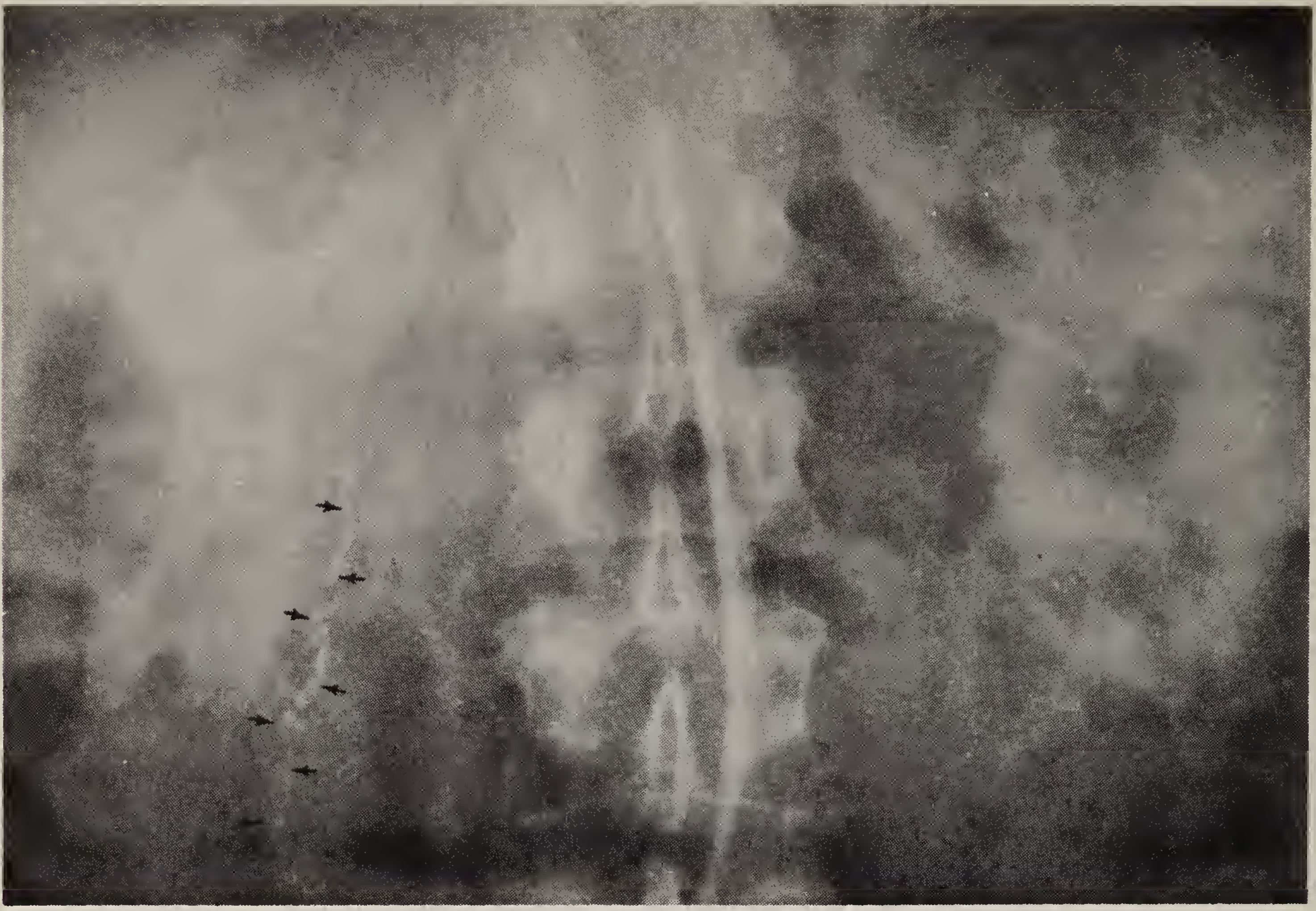

Fig. 14.—Delayed arteriogram showing tortuous ureteral artery (ARROWS) supplying the right kidney. This produces notching of the ureters. (Same patient as Figures 6 & 8.)

SUMMARY

The excretory urogram is a means of assessing unilateral renal vascular compromise, both physiologically and morphologically. The renal arteriogram defines the exact site and morphologic nature of the process. Both procedures are indispensable in the study of hypertension but are only complimentary to the host of other physiological tests necessary to decide which vascular lesion is producing a surgically curable hypertension.

THE MEDICAL TREATMENT OF ESSENTIAL HYPERTENSION

Henry D. DeYoung, M.D.

Roger R. Schuessler, M.D.

The goal in treatment of hypertension is to discover and treat the basic pathologic condition. Conditions that must be searched for are those which can produce both a systolic and diastolic hypertension. They include pheochromocytoma, unilateral parenchymal renal disease, extrinsic renal vascular disease, primary hyperaldosteronism, adrenal cortical hyperfunction, Cushing's syndrome, pituitary tumors, brain tumors, coarctation of the aorta, and eclampsia. Diseases such as thyrotoxicosis, arteriovenous fistula, complete heart block, and anemia, which produce only a rise in the systolic pressure should also be kept in mind. This discussion presupposes that specific etiologies for hypertension have been excluded prior to the initiation of any therapy.

During the past decade medical treatment of hypertension with antihypertensive drugs has become a challenge to the physician. Prior to the availability of a variety of effective agents, surgical sympathectomy was the only practical means of lowering blood pressure. Currently the physician must decide which drugs to employ and, equally important, which patients to treat.

It has been established that the hypertensive patient has a decreased life expectancy.[1] The greatest threats to his longevity are accelerated atherosclerosis, arteriolosclerosis, myocardial hypertrophy and dilatation. When antihypertensive agents were first used many believed that this cardiovascular degeneration represented the primary disease state with hypertension being a result rather than the cause. It now seems certain that the elevated blood pressure is largely responsible for the hypertensive vascular disease regardless of the etiology of the hypertension.[2] There is considerable evidence that these secondary cardiovascular lesions may be prevented or arrested with antihypertensive treatment. Patients vary greatly in their susceptibility to these complications, making an evaluation of the effectiveness of antihypertensive therapy difficult.

There is evidence that life expectancy in patients with severe hypertension is prolonged with treatment.[3,4] It is in the milder hypertensive, where prognosis is relatively good, that the benefits of treatment are more difficult to assess. It would be unfortunate to subject a patient to antihypertensive therapy without altering his prognosis. However, it would be more unfortunate to withhold therapy if real benefit might be expected. The need for treatment increases as the patient's prognosis becomes worse. Factors that point to an unfavorable prognosis are progressive organic damage, high diastolic pressure, male sex and young age. Women generally tolerate hypertension better than men and Caucasians fare a bit better than Negroes. The most im-

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From the Department of Medicine

portant signs of organic damage are retinopathy and renal impairment. A hypertensive patient with advanced complications such as uremia or coronary or cerebrovascular sclerosis may no longer be benefited or may even be harmed by vigorous treatment.

PATIENT SELECTION

At the present time an estimate of the patient's prognosis appears to be the best guide to therapy. The selection of specific antihypertensive drugs makes it convenient to divide treatable patients into two categories, a) those with a clinically favorable prognosis, namely with little or no evidence of systemic complications and whose diastolic blood pressure is usually not above 110 mm. Hg and b) those with moderate or severe hypertension, namely with definite manifestations of systemic complications and whose diastolic blood pressure is usually above 110 mm. Hg. A young male with a diastolic pressure consistently above 110 mm. Hg., early retinopathy and perhaps slight proteinuria represents the ideal candidate for treatment. A female over 50 years of age with diastolic pressures below 110 mm. Hg without signs of organic damage represents the other end of the spectrum and treatment would not be warranted. The elderly patient with only a systolic elevation of blood pressure with a normal diastolic level does not need specific antihypertensive therapy.

The physician caring for a hypertensive patient must treat not only the sphygmomanometer reading but the individual, both his physical and emotional being. It has been reported that following long periods of successful antihypertensive therapy the blood pressure level may be reset to normal.[5] The physician should therefore approach the patient with an attitude of hope and not despair. A good doctor-patient relationship is of utmost importance. The tense, anxious patient may be greatly benefited with small doses of phenobarbitol or tranquilizers such as meprobamate. The obese patient needs adequate explanation of the importance of weight reduction. He should be given a low calorie diet tailored to his own dietary habits, given with understanding. Of real significance is sodium restriction for all moderate or severe hypertensive patients.

It is important to realize that the truly valuable blood pressure readings are the so-called basal blood pressures. However, in the ambulatory treatment of hypertension, the casual or office blood pressure readings must be relied upon. These can be of definite value if decisions are based not upon the initial reading, but upon repeated determinations both at the beginning and the end of several outpatient visits.

The clinical approach to drug therapy for the hypertensive patient demands an outline of therapy based on the severity of the hypertension as correlated with the blood pressure lowering effect of the agent or agents employed. A division of the useful antihypertensive drugs into three classes seems convenient, a) those with mild to moderate blood pressure lowering effect, b) those with definite but not marked blood pressure lowering effect, c) those with marked blood pressure lowering effect to the point of production of orthostatic hypotension and syncope.

MILDLY EFFECTIVE DRUGS

Benzothiadiazine Diuretics: These agents act upon the proximal and distal convoluted tubules to increase the excretion of sodium, potassium, and chloride. They initially induce a negative sodium balance lasting for approximately 48 to 72 hours. The sodium loss is derived from the total extracellular fluid producing a reduced plasma volume. Following this the moderate hypovolemia results in a decreased cardiac output.[6] After the initial salt depletion compensatory mechanisms of an unknown nature prevent further depletion. The plasma volume, total extracellular volume and cardiac output return partially to normal, however, the blood pressure remains moderately reduced on long term administration. The Benzothiadiazine diuretics have not only a modest intrinsic antihypertensive effect, but are quite useful when combined with other agents to enhance further blood pressure reduction. The most commonly used agent in this group is Chlorthiazide (Diuril)®. Other benzothiadiazine diuretics differ from this only in potency and duration of action. The various compounds can be used interchangeably and no compound has a significant advantage in either lessened toxicity or effectiveness. The usual initial dose of Chlorthiazide is 500 mg twice daily, however, the response to the dosage schedule varies and some individuals may respond equally well to a smaller dose. The toxic effects of the benzothiadiazine diuretics include dermatitis and bone marrow depression with thrombocytopenia. Hyperglycemia is known to occur, however, ketosis is generally not present. Hyperuricemia to the point of appearance of clinical gout is described.[7] The most common side effect is hypokalemia.

Rauwolfia Serpentina: This class of drugs reduces the catecholamine content of the tissues in laboratory animals. They not only deplete cerebral stores but to a great extent peripheral stores of norepinephrine. Thus their main blood pressure lowering effects may be peripheral, rather than in the hypothalamus as originally believed.[8] The most widely used alkaloid of Rauwolfia Serpentina is Reserpine®. It is a mild antihypertensive compound and in addition exhibits a tranquilizing effect. The usual initial dose of Reserpine® is 0.5 to 1.0 mgms daily for a week or two and thereafter 0.25 mgm daily or less. With Reserpine® the cardiac output, renal and cerebral blood flow are not reduced and postural hypotension does not occur. The maximal antihypertensive effect of Reserpine® is obtained slowly over the course of several weeks. The most common side effects of the Rauwolfia Serpentina compounds are nasal congestion, drowsiness, and nightmares. Occasionally severe depression may occur, and the patient should be warned of this possibility. Occasionally, due to the unopposed para-sympathetic activity, these compounds may produce increased frequency of defecation or loose stools. It is important that these compounds be discontinued prior to general anesthesia since severe hypotensive episodes have occurred.

Hydralazine (Apresoline®): This compound reportedly acts by reducing peripheral resistance. The exact hypotensive action is not fully understood. Hydralazine, however, simultaneously increases cardiac output and renal blood flow.[9] Hydralazine should not be used as a drug of first choice, however it may be of modest value when used in combination with other agents. Its effectiveness appears to be quite variable. The usual oral dose is initially 20 to 40 mgms daily which may be increased gradually to an effective level not greater than 200 mgms daily. Early side effects include headaches, nausea vomiting, palpitation, dizziness and weakness. These are ordinarily transitory and diminish as treatment is continued. Hydralazine may, by a direct cardiac effect, produce electrocardiographic evidence of ischemia and anginal attacks.[10] Prolonged large doses may produce a rheumatoid arthritis-like state and also a syndrome indistinguishable from acute lupus erythematosis. However doses of 200 mgms or less are relatively safe.

MODERATELY EFFECTIVE DRUGS

Alpha-Methyl DOPA (Aldomet®): This drug represents a new approach to the control of hypertension. It is a methylated derivative of the naturally occurring amino-acid dihydroxyphenylalamine. It was designed to competitively interfere with the biosynthesis of norepinephrine, however, this mechanism of action has not been confirmed.[11] Alpha-methyl DOPA is believed to interfere with the synthesis, storage or activity of norepinephrine and other amines.[12] There are varying opinions about its effects on the vascular system, but it appears likely that arterial pressure is reduced largely by a decreased cardiac output.[13]

Alpha-Methyl DOPA appears to be an effective hypotensive agent. It produces a smooth lowering of blood pressure and its effect on supine blood pressure is probably greater than that of Guanethidine. However, some hypertensive patients are unresponsive and in some series treatment was abandoned in as many as one third of the patients.[14] The initial dose of alpha-methyl DOPA is 25 mg. two or three times daily. The usual effective dose is 750 to 2000 mg. daily in divided doses. The hypotensive effect may be cumulative and therefore the dose should not be increased oftener than every 3 days. Alpha-Methyl DOPA is eliminated by the kidneys and in the presence of renal impairment the dose must be reduced accordingly. The drug has not been used extensively enough to accurately assess the true incidence of side effects. During the first few days of treatment a transient sedative effect is often observed. Other reported side effects are mental depression, edema, gastrointestinal symptoms, dry mouth, dizziness, changes in liver function tests and reversible leukopenia. The manufacturer recommends liver function tests and blood counts be done at intervals during the first 2 months of therapy and also if unexplained fever should occur.[15]

MARKEDLY EFFECTIVE DRUGS

Guanethidine (Ismelin®): Guanethidine has two modes of action. The primary action is on the sympathetic nervous system with a blockade of adrenogenic neurones. Its action is confined to the peripheral sympathetic nervous system since it does not cross the blood brain barrier. It also acts partly by depleting tissue catecholamines.[16] Its hypotensive effect occurs as a result of inhibition of vasoconstrictor responses. The cardiac output is decreased and the total peripheral resistance is reduced. These effects are similar to those of the ganglion blocking agents without the troublesome effects of parasympathetic blockade. Its onset of action is slow with a long duration of action. A single dose may produce an effect for 5 to 7 days. Tolerance does not develop and it is clinically as potent as any present day hypotensive drug. The dose of guanethidine varies widely from patient to patient, varying from 10 mg. to greater than 300 mg. daily. In view of its slow and prolonged action, on initiation of therapy the dose should not be increased oftener than every 5 to 7 days in order to avoid hypotension. The side effects of guanethidine include orthostatic hypotension, failure of ejaculation and diarrhea. Weight gain, edema and mental depression have also been described. However, once an optimum dose has been established, the side effects have been minimal with a maintained hypotensive response. The drug should be discontinued several weeks prior to elective surgery. In the event of the necessity of emergency anesthesia, norepinephrine must be available.

Ganglionic Blockers: The ganglionic blocking agents include hexamethonium, pentolinium tartrate (Ansolysen®), chlorisondamine chloride (Ecolid®), and mecamylamine (Inversine®). These drugs block autonomic ganglion transmission, both parasympathetic and sympathetic by inhibition of acetylcholine. Since sympathetic vasoconstrictor nerves control venular as well as arteriolar tone, the ganglionic blockers not only reduce arteriolar resistance but also increase venous capacity. This increase in venous capacity reduces right heart filling pressure and thus in compensated patients the cardiac output decreases. However, in heart failure the cardiac output may actually be increased due to reduced aortic pressure.[17]

A superiority of one blocking agent over another has not been definitely demonstrated, however, mecamylamine (Inversine®) has the advantage of more complete absorption on oral administration, and a prolonged action. These drugs with parasympathetic action are now used less frequently since guanethidine has become available. The incidence of side effects such as constipation, fatigue, dry mouth, anorexia, urinary retention, and paralysis of visual accommodation (due to parasympathetic blockade) as well as orthostatic hypotension may be greatly reduced by the addition of a saluretic agent allowing a reduced dose of the ganglionic blockers.

Since hypertensive emergencies are a unique clinical complication, it seems desirable to summarize their therapy briefly prior to our outline of a plan for hypertensive management.

HYPERTENSIVE EMERGENCIES

Hypertensive encephalopathy is a medical emergency which demands prompt treatment. It may occur in either a general form or a focal form. The general form is characterized by headache, vomiting, stupor, coma, stertorous breathing and papilledema as well as convulsions. This form is frequently seen in acute hypertensive states such as eclampsia and acute glomerulonephritis. The focal form is more usual in patients with long standing severe hypertension. In this form, hemiparesis, convulsions, and coma are common. This form is easily confused with a cerebral vascular accident.

In the drug therapy for this emergency it is well to remember the efficacy of a time honored drug, magnesium sulfate. In children and in a small percentage of young adults an intramuscular injection of a 50% solution in a dose of 0.2 mg. per Kg. of body weight will adequately lower diastolic pressure. If used intravenously a 3% solution of hydrated magnesium sulfate may be given slowly up to a dose of 150 mg. per Kg. of body weight over a period of one hour.

Reserpine® is a valuable agent in the therapy of hypertensive encephalopathy when given intramuscularly in doses of 2 to 10 mg. The maximum blood pressure lowering effect is not reached for a period of two to three hours after either an intramuscular or intravenous injection. There is, therefore, no great advantage to the intravenous route.

If a more rapid hypotensive effect is desired other agents such as the ganglionic blockers are desirable. These drugs, if given for longer than a day, are usually associated with undesirable parasympatholytic effects such as dry mouth, blurred vision, urinary retention and constipation to the point of paralytic ileus. The paralytic ileus can be treated with neostigmine subcutaneously in doses of 1 mg. per hour until peristalsis is again established. Postoperative patients are particularly susceptible to the parasympatholytic effect of these drugs and thus these agents should be avoided in the postoperative period if possible. Ganglionic blockers reduce the venous pressure and therefore are quite valuable in patients with congestive heart failure who exhibit encephalopathy. The usual doses for the ganglionic blockers are—chlorisondamine chloride (Ecolid®) 2.5 to 25 mg. intramuscularly; pentolinium tartrate (Ansolysen®) 2.5 to 5 mg. intramuscularly, 5 mg. in a 20cc volume intravenously, or 50 to 150 mg. per liter in a titrated intravenous drip; and trimethaphan camphor sulfonate (Alfoned®) 1000 mg. per liter as an intravenous drip.

Sodium nitro-prusside will consistently lower blood pressure in hypertensive encephalopathy of any origin.[18] Its hypotensive effect is almost immediate when given by intravenous infusion and is reversible just as quickly when the infusion is stopped. The usual dose is 60 mg. per liter given at the rate of 10 drops per minute. The rate of infusion and concentration can be titrated to maintain the desired blood pressure level and prevent side effects such as vomiting, retching, muscular twitching, agitation, and diaphoresis.

Phentolamine (Regitine®) is the specific agent in treating the hypertensive crisis caused by pheochromocytoma. In this instance the drug should be administered rapidly intravenously, beginning with a 5 mg. dose and repeating or increasing the dose until the crisis is controlled.

It is well to remember, that in the therapy of hypertensive emergencies, it is usually not desirable to reduce the blood pressure level below 160 mm. Hg. systolic and 100 mm. Hg. diastolic, particularly in the middle or older age groups. This is an attempt to avoid cerebrovascular accidents, myocardial infarction, or rising azotemia in individuals with severe renal damage.

PLAN OF THERAPY

When it has been determined that drug therapy is indicated in the management of a hypertensive patient we follow this general plan.

The initial drug used is chlorothiazide. The milder hypertensive patient may respond well to this and, if not, it provides the base for the addition of other drugs. If the combination of drugs in the "mild" group does not adequately lower the blood pressure Reserpine® and hydralazine are discontinued and alpha-methyl DOPA is added to the chlorothiazide. If this proves ineffective the alpha-methyl DOPA is discontinued and guanethidine is used in combination with chlorothiazide.

INITIAL DRUGS	SUBSEQUENT ADDITIVE DRUGS
MILD HYPERTENSION: Chlorothiazide (Diuril®)	Reserpine (Serpasil®) Hydralazine (Apresoline®)
MODERATE HYPERTENSION: Chlorothiazide (Diuril®)	Alpha-methyl DOPA (Aldomet®)
SEVERE HYPERTENSION: Chlorothiazide (Diuril®)	Quanethidine (Ismelin®)

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HYPERTENSION OF RENAL VASCULAR ORIGIN

JAMES A. HUNTER, M.D.
ORMAND C. JULIAN, M.D., PH.D.
WILLIAM S. DYE, M.D.
HUSHANG JAVID, M.D., PH.D.

As long ago as 1836, Bright[1] related hypertension to disease of the kidney. Since that time the problem of pathologic blood pressure elevation has been subjected to much investigation with emphasis on renal related humeral mechanisms. Renin and VEM (vasoexciter material) have been extensively studied in the laboratory and their roles postulated. Goldblatt demonstrated in 1934[2] that renal ischemia as produced in the experimental animal results predictably in hypertension, a work that remains one of the best known and most important of basic investigations.

Many patients with hypertensive disease defy specific etiologic diagnosis, despite the fact that investigation and clinical observation have established a substantial list of pathologic states known to be associated with hypertension. Although the medical treatment of abnormal blood pressure elevation has achieved a status of value and worth, such management has numerous limitations and is never characterized by cure. Hypertensive patients are cured, however, and the serious cardiac, ocular, cerebral, and vascular complications arrested or prevented when a specific etiologic diagnosis can be made and appropriate surgical measures applied. Among such causes of hypertensive disease, wherein the basic etiology can be ascertained and surgical cure then often effected, are coarctation of the aorta, pheochromocytoma, aldosterone-secreting adenoma of the adrenal glands, and lesions of the extra-parenchymal renal vessels that affect blood flow. It is our purpose in this publication to consider the subject of renovascular hypertension, a subject of particular importance because of its greater incidence than other potentially curable hypertensive diseases and also because this entity has only recently been given proper emphasis.

Prior to the current decade with its renewed interest in renovascular hypertension, there was distinct disappointment regarding surgical procedures for abnormal blood pressure elevation. Nephrectomy was applied for unilateral disease of the kidney, but the cure rates at best in published series failed to exceed 26%[3,4]. Recently interest has been renewed in this field because of a much improved understanding of the pathophysiology of of renal hypertension, the availability of better diagnostic techniques, and the development of cardiovascular surgery with its technical skills. These factors have served to vastly improve results following surgical procedures designed to relieve hypertension.

From the Cardiovascular Section, Department of Surgery, and the University of Illinois Research and Educational Hospital.

Lesions that affect either total renal arterial blood flow, or renal arterial pulse pressure[5,6] so alter the hemodynamics that a proteolytic enzyme, renin, is released by the kidney which in turn participates in a series of reactions involving a hepatic protein substrate, and finally results in the formation of a very potent vasopressor substance (Angiotensin). Such lesions include renal artery stenosis, renal arteriovenous fistula, renal artery occlusion, and aneurysms of the renal artery. By far, the commonest lesion of these four is renal artery stenosis. The object of surgical treatment is to relieve the mechanical factor responsible for the chain of events resulting ultimately in the circulating vasopressor substance.

Renal Artery Stenosis

Following Goldblatt's publication the subject of renovascular hypertensive disease received only little attention in the medical literature until the publication of Poutasse and Dustan, 1957[7]. More recently numerous publications have been devoted to the subject[8-11] and the total number of cases reported has rapidly increased.

Etiology: At least ten different causes of renal arterial stenosis have been reported in the literature (12), but the majority of cases encountered have one of three etiologies; namely, focal arteriosclerotic disease, fibromuscular hyperplasia, or simple idiopathic congenital stenosis, listed in the order of frequency. The true incidence of hypertension due to renal artery narrowing is unknown, but as is the case with any entity in which the profession has found only recent interest, the number of cases will increase with the knowledge and index of suspicion of the individual physician. The diagnosis has been made in all age groups from infancy (10) to patients in their eighth decade of life.

Circumstances which should in particular direct the physician's attention to hypertension of this etiology include (1) children or young adults with significant hypertension; (2) hypertension of recent onset; (3) severe hypertension that rapidly progresses to the malignant phase; (4) malignant hypertension in the older age group; (5) elevated blood pressure in patients with a history suggestive of renovascular accident; (6) hypertension in a patient with known arterial disease elsewhere in his vascular tree; (7) mild hypertension that suddenly becomes severe, and (8) the entity must be considered in any patient with significant hypertensive disease where the abnormal blood pressure is affecting a favorable prognosis for life and well being.

Diagnosis: The general physical examination of the hypertensive patient with renovascular disease most often will not permit definitive diagnosis. It will, however, enable the examiner through the evaluation of eye grounds, heart size, and peripheral vascular tree to gain some insight as to the physiologic importance of the hypertension. Signs of arteriosclerotic disease should be looked for, such as a bruit over an iliac or femoral artery as, though this finding may be of no local importance, it should be recognized in passing that the same arteriosclerotic disease resulting in arterial irregularity which produces the bruit may have similar involvement at the orifice of a renal artery. The anterior and posterior renal areas should be carefully auscultated, as one may be rewarded with the finding of a systolic bruit produced by the turbulence in the stenotic renal artery. This finding has often been present in patients with fibromuscular hyperplasia of the renal artery. The absence of such a bruit in no way, however, depreciates the possibility of renal arterial abnormality.

Routine laboratory investigations of the patient are usually negative with the urinalysis and urea nitrogen being normal[10,13,14]. Chest x-ray and electrocardiogram serve to give further clues as to the physiologic importance of the hypertension. An infrequent patient may evidence azotemia if there is severe bilateral arterial obstruction.

The intravenous pyelogram is an important study. In patients with hypertension, films of the renal areas are obtained at 30 seconds and 2 minutes, in addition to the standard 5 minute films, so as to obtain a nephrogram and record the early appearance of the dye. Although it does not invariably do so, the kidney with arterial involvement may show a phase of delayed excretion on these early films that would be missed if the standard 5 minute film were the first. Occasionally the involved kidney will be significantly smaller than its partner, and more exceptionally the ureter, as viewed with contrast material within it, may show notching due to the development of collateral renal arterial flow. It is important to emphasize, however, that in the classical instance of renovascular disease this examination is completely normal.

After preliminary investigations, examinations of a specialized sort may be indicated to further evaluate the hypertension. These studies are three: the radioisotope renogram; studies of differential kidney function, and renal arteriography.

The simplest of the specialized examinations is the radioisotope renogram. This test is easily performed, can be done on an out-patient basis, the amount of radiation received is minimal, and the cost is low. The study involves administering intravenously a radioisotope tagged substance such as Hippuran, and then recording the appearance and intensity at the renal areas. The gamma irradiation can be counted and charted in relation to time, and the two sides compared. The initial peak of appearance relates directly to renal blood flow and has particular importance. The examination is especially valuable in comparing the two sides, and it is expected that it will become the principal study used to screen candidates for aortography.

Popularized clinically by Howard, et al,[15,16], was the demonstration that in the instance of renal ischemia electrolyte excretion by the kidney is decreased. In particular, less sodium is excreted and the total volume output of that kidney is also diminished. When renal artery lesions are suspected, the ureters are intubated and urine is collected separately from the two kidneys, enabling the evaluation of the excretory function of each and permitting performance of split function studies. Modifications of this examination have been proposed and employed by Stamey with improved results. As with the radioisotope renogram, the most impressive results are obtained in patients with unilateral disease, where there is opportunity to contrast the sides. The data is especially helpful to the surgeon because it provides information about function to be considered in light of subsequent deformities demonstrated by arteriography, and aids in interpreting the significance of questionable findings on the angiogram.

Essential before diagnosis can be conclusively established, and an operative prerequisite, is aortography. All of the examinations by virtue of their positive or negative results will reflect on the probability of there being a renovascular lesion, but it remains for the aortogram to demonstrate it. Indeed, only the arteriogram permits positive diagnosis, defines the anatomy of the lesion, directs treatment, and permits speculation as to prognosis. An aortogram should be performed on any patient who has historic, physical, or laboratory findings that may suggest the diagnosis and probably in the majority of patients who have systolic-diastolic hypertension of demonstrated physiologic importance and an altered prognosis.

In the experience of the authors, and of others reported in the literature, aortography has been accomplished with little risk and with excellent results in terms of data obtained[5,17]. Two methods are employed: the translumbar percutaneous needle puncture of the aorta, and the retrograde method through a femoral artery. Both methods have their advantages and disadvantages. The lumbar approach is rapid and convenient, but makes changing of the level of aortic injection or altering the position of the patient in relation to the x-ray film difficult. Lumbar aortography should not be employed when studying children. The retrograde femoral aortogram bears the advantage of complete mobility as to the point of injection and ease of patient positioning, but should not be performed in patients with arteriosclerotic change in the iliac, femoral, or lower extremity arteries. The studies are generally done under local anesthesia, except for children where general anesthesia should be employed. It is desirable to use x-ray equipment that will permit multiple exposures during the single injection so that the complete renal vascular tree may be visualized, including the small secondary branches. Interpretation of the films generally is not difficult. The most common lesion due to arteriosclerosis results in stricture of the artery at its origin at the aorta, whereas obstructions due to fibromuscular hyperplasia typically involve the central third of the main renal artery or less commonly one of its secondary branches. Often, post-stenotic dilatation is seen distal to the point of narrowing and serves to differentiate true anatomic deformity from artefact or spasm. Occasionally it is helpful to review the physiologic studies when interpreting the anatomy portrayed in the arteriogram.

Therapy: Once the diagnosis of renovascular disease has been made, surgical treatment will in almost all cases be appropriate. Medical management of such patients, of course, never results in total relief of the disease and, indeed, drug management of this particular group of hypertensive patients is said to be less effective than the response of the unselected patient with idiopathic hypertension. In keeping with the fact that this is an era of reconstructive vascular surgery, the principle has been one of repair of the arterial lesion, rather than removal of the kidney. The surgeon does have a choice, except in bilateral lesions, of either removing the involved kidney or effecting a repair of the artery. The most desirable procedure is, however, restoration of normal arterial blood flow for the following reasons: (1) in bilateral disease this is the only method available. (2) A maximum of functional renal tissue is preserved. (3) The kidney supplied by the involved artery may be the better kidney in terms of its parenchyma.

The above statement regarding the renal parenchyma recognizes the fact that there is unquestionable evidence indicating that the involved kidney which has produced the hypertension is actually protected from the impact of the blood pressure elevation by the same lesion that has caused it. There is, of course, no such mechanism to protect the contralateral organ. Histologic studies from the two kidneys in instances of unilateral disease have shown significant arteriolar nephrosclerosis on the side with a normal arterial anatomy and the absence of such changes on the side of vascular constriction[5,13,18,19,20]. Because of the parenchymal change in the kidney without a lesion in its main artery, delayed or even incomplete response of the blood pressure reduction following operation may be seen. In instances of bilateral renal artery stenosis, where there has been protection of the parenchyma bilaterally from the hypertension and the perpetuating factor of unilateral nephrosclerosis is not present following operation, a normotensive state is promptly achieved after operation more consistently. It follows that a case should be encountered where the successful restoration of normal blood pressure will only follow reconstruction of the narrowed artery and then opposite nephrectomy. Such a case has only very recently been reported[21].

Indications for nephrectomy are two. First, in the treatment of a very old patient with unilateral disease who is a grave surgical risk, and two, in the management of an anatomically unfavorable arterial lesion such as that presenting several areas of stenosis in the patient with multiple small renal arteries. Fortunately, these two circumstances are infrequently encountered. Extra-peritoneal nephrectomy is a simpler and more rapid procedure in the critical patient.

A variety of methods and techniques of arterial reconstruction have been reported. The methods of repair that we have most often employed include the use of a by-pass graft between the aorta and renal artery distal to the stenosis, division of the artery with adjacent reimplantation on the side of the aorta, longitudinal sectioning of the stenotic artery and then application of an onlay patch graft to enlarge the circumference, endarterectomy of the involved segment, and perhaps the method of choice in the favorable lesion, resection of the stenosis with end-to-end anastomosis of the artery. Splenorenal arterial anastomosis is described in the literature[11] and although the technique is an effective one, we have not employed it because simpler methods of reconstruction have always been feasible. Operation is performed under systemic hypothermia because of the added safety factor which it provides, even though the customary period of renal arterial clamping does not exceed 15 minutes. The surgical approach of preference, regardless of the reconstructive technique that is to be employed, is anterior and transperitoneal. A long midline or paramedian incision is used. Flank or transverse incisions have been found to be distinctly less satisfactory. After the peritoneal cavity has been generally explored, the transverse colon and the small bowel are respectively lifted up and out of the wound superiorly and laterally, providing the operator with direct exposure of the posterior peritoneum. The abdominal aorta is then exposed through an incision over it, placed between the root of the small bowel on the right and the inferior mesenteric vein on the patient's left. Dissection upward soon reveals the left renal vein at the point where it crosses anteriorly over the aorta, and this structure serves as a guide to the probable level of the renal artery origins from the aorta. The previously obtained aortogram will at this point direct the surgeon in terms of the number and locale of the individual renal vessels. Exposure of the main renal artery is then achieved bilaterally by dissecting out their lengths after identifying their origins from the side of the aorta. Occasionally exposure of the extreme distal divisions of the main artery may be better achieved with extra-peritoneal dissection beginning at the pericolic gutter on either side. Any portion of the right or left renal artery may thus be exposed by this route. Most stenoses occur either at the origin of the main artery or between this point and its first bifurcation, so that exposure in the average case is not difficult. After exposure the narrowed segment is examined and the distal, generally dilated segment palpated to elicit the presence of a thrill or diminished pressure. At this point actual pressure determination is performed by puncturing the artery proximal and distal to the stenosis with a needle connected to sensitive electronic equipment which will permit the determination of even a minimal gradient. The character of the arteries under consideration and the anatomic locale of the lesion are then carefully considered and the method of surgical repair decided upon. One is very much more restricted in the selection of a method of reconstruction in children, because of the need to avoid the use of prosthetic materials. In the pediatric age group where there is a significant growth potential, the principle of resection of the stenosis with end-to-end anastomosis or division of the artery beyond the stenosis and reimplantation on the side of the adjacent aorta should be used. Anastomoses are performed using fine sutures and interrupted technique. For example, a long segmental stenosis in the main renal artery of a 4-year-old where the area of narrowing was too long to permit resection and re-approximation, the principle of longitudinal section and the placement of an onlay autogenous venous graft was used to provide a normal lumen[22]. The vein graft was obtained from the patient's internal iliac system.

The most common etiology of renal artery stenosis is focal arteriosclerotic change, and when treating this lesion the method of choice is either endarterectomy or division of the vessel distal to the stenosis and reimplantation on the adjacent aortic wall. When the aorta adjacent to the origin of the renal artery is thickened and abnormal in the entire general area of the renal vessel, the very effective alternate technique of by-pass grafting has been used as the most common method of reconstruction.

In instances of bilateral renal artery stenosis, or when the surgeon is treating associated disease of the abdominal aorta itself, such as arteriosclerotic abdominal aortic aneurysm, then by-pass technique becomes by far the most practical one. A 10 mm. diameter crimped Dacron tube is first anastomosed end of the prosthesis to the side of the aorta, and then after completion of this suture line, the end of the graft is sutured to the side of the renal artery beyond the area of obstruction. When both renal arteries are involved, a small bifurcation graft will permit bilateral treatment with but three arterial anastomoses required. The by-pass grafts, as described, do have a number of desirable features. First, the method is the simplest, most rapidly executed and adaptable of the techniques available for the treatment of the average case. Second, the time of interruption of renal arterial flow is kept to a minimum, and third, because the grafts are short, are not subject to angulation or motion, and are contained of very high rates of arterial flow, there is a strong tendency toward long term patency and function. After arterial reconstruction, by whatever method selected, has been completed, pressures should be again obtained in the involved arteries to be certain that the gradient has been totally abolished. Bilateral kidney biopsies should be obtained, as these may be of value in the future management of the patient.

Results: The results of the surgical treatment in terms of control of the hypertension in properly selected cases have been gratifying. On occasion the immediate or late results of surgery have been most dramatic. For example, we have seen a 2-year-old child with hypertensive heart disease in failure respond so perfectly to surgery that heart size returned to normal and Digitalis could be dispensed with. Even more immediate, we have observed systolic blood pressure fall from 280 mm. of mercury to 120 mm. four hours after operation and remain at this new level. Pressure response may be slower or even incomplete in the patient with unilateral disease, because of opposite parenchymal involvement. The renal biopsies that are obtained, as mentioned above, may help to clarify the reason for imperfect results, and may in highly selected cases direct further operative management. Very infrequently after repair of the stenosed artery and where the blood pressure has failed to respond, opposite nephrectomy of the "good kidney" may be indicated after thorough evaluation of the success of the arterial repair and the review of biopsies obtained at surgery. The favorable response in the majority of patients of the cardiac, cerebral, and even ocular complications[23] of the hypertension to its control has been well demonstrated. Reported results[5,9], and those of our own, indicate that with proper case selection and with the application of the principle of arterial reconstruction, hypertension can be relieved in excess of 80% of cases.

Renal Arteriovenous Fistula

Varela[24] reported the first case of renal arteriovenous fistula in 1928, the patient being a 28-year-old male with hypertension, dyspnea, cardiomegaly, and a bruit in the flank. Twenty-five instances of this rare entity have appeared in the literature since the first case report[25].

Etiology: The majority of the reported patients have had a congenital etiology for their fistula, such as the first patient of Varela, and that of Slominski-Laws[26] from the University of Illinois Hospital. Acquired lesions have had multiple causes, including trauma[27,28], fistula formation secondary to rupture of an arterial aneurysm[29], and secondary occurrence to neoplasm[30].

Diagnosis: Hypertension has usually accompanied the presence of the lesion, but not always so. Cardiac sequelae of the arteriovenous fistula have been prominent in the cases reported. It is considered that the altered renal arterial blood flow with disturbed pulse pressure in the renal artery has resulted in Goldblatt's phenomenon. Despite the fact that the lesion is of infrequent occurrence, it is important because the presence of a continous thrill or bruit in the renal area on physical examination has been exceedingly common, permitting bedside diagnosis in the afflicted patient. Two of the reported cases have been encountered on the surgical service of the University of Illinois and both have had this finding.

Aortography should define the presence of the lesion if the patient is so studied. A widely dilated and extremely tortuous renal artery was seen in the most recent patient studied at the University of Illinois, and this typical finding in any arteriovenous fistula should provide a clue when seen on the arteriogram. Venous oxygen saturation in samples of blood obtained from a catheter introduced into the inferior vena cava at the level of the renal vein should in a suspected case provide diagnostic information.

Therapy: Relief of the hypertension can be anticipated, on the basis of data from the literature, by nephrectomy. One of the patients treated at the University of Illinois did, however, not have a complete response in terms of reduction of his blood pressure following operation, but did for the first time become responsive to hypertensive drugs. It is considered likely that this patient's opposite kidney by virtue of its arteriolar change secondary to the hypertension is perpetuating the blood pressure elevation. It has not been possible to treat any of the reported cases by direct arterial repair, due to the fact that the majority of them have had renal parenchymal involvement by the fistula.

Renal Artery Aneurysm

Approximately 143 instances of renal artery aneurysm were reported in the literature as of 1959, in a summary made by Glanton and associates[31]. The over all incidence of this uncommon lesion is from 0.1 to 0.15% based on autopsy studies or 1% of all aneurysms[32].

Etiology: The etiology may be trauma, arteriosclerosis, infection, or a congenital deficiency in the arterial wall. Most of the aneurysms are saccular in type. There has been no sex predilection or tendency toward right or left side of preferential occurrence. The majority have occurred during the fourth and sixth decades of life, but cases have been reported from childhood through advanced age. Most of the lesions have occurred in the distal main artery or just beyond the primary bifurcation[33].

Diagnosis: Hypertension is said to occur in only 15 to 20%[32,34] of all cases reported, and it is clear from the literature that the presence of hypertension in a patient with a renal artery aneurysm does not definitely indicate a cause and effect relationship. Microscopic or gross hematuria has been recorded as a frequent finding with an incidence of about 35%.[31]

In addition to interfering with blood flow through the renal artery and the resulting Goldblatt phenomenon, complications of the aneurysm are two; namely, renal infarction[31,35] or, more commonly, rupture[36]. Mortality may be high with retroperitoneal disruption of the lesion[37]. A-V fistula has resulted from rupture of the aneurysm into the adjacent vein[29].

A calcific outline of the aneurysm may be seen on plain films, as is commonly the case with a splenic artery aneurysm. However, less than one-third of lesions will present this finding[38]. The pyelogram may show distortion of the kidney if the aneurysm is large, and aortography should reliably define the aneurysm.

Therapy: To treat hypertension, prevent thrombosis with renal ischemia, and, quite important, to prevent rupture of the aneurysm, treatment should usually be surgical. Arterial reconstruction should be performed with renal preservation when the anatomy of the lesion lends itself to such management[39]. In instances of unfavorably located lesions, which are unilateral, a nephrectomy should likely be performed. If the aneurysm has been obstructing arterial flow and hypertension has resulted, a favorable result in terms of the blood pressure can be anticipated. It should be recalled, however, that all hypertensive patients with such a lesion may not have their blood pressure elevation on the basis of the presence of the aneurysm[33,34]. The data from the literature would indicate caution in this regard, and therefore, conservatism in predicting relief of hypertension by surgical eradication of the lesion.

Renal Artery Thrombosis

Etiology: Acute obstruction or thrombosis of a renal artery may result either from thrombosis of a previously diseased and narrowed channel, or may be due to embolic phenomenon[40,41].

Diagnosis: Total infarction of the kidney does not result in hypertension, but subtotal infarction or ischemia may give rise to severe hypertension which can terminate in the patient's death[42]. Typically, such acute ischemia is characterized by flank pain, hypertension, and in about half of the cases occult or frank hematuria[43]. We have recently seen a patient who suffered acute thrombosis of the renal artery to her only kidney, the onset being heralded by acute flank pain and anuria. Although it was possible technically to repair the obstructed artery and restore blood flow to the renal parenchyma in this case, irreversible renal ischemia had developed prior to operation and the patient expired with progressive uremia. Abrupt flank pain associated variably with hematuria, hypertension and oliguria or anuria should cause one to consider an acute renovascular accident in the differential diagnosis.

Specialized studies will include intravenous and retrograde pyelography. The former will show variable results depending upon the total degree of infarction, but often there will be nonvisualization. Pyelography performed by retrograde catheterization of the ureter will usually be normal during the early period. The diagnosis of renal artery arterial occlusion should be possible in the majority of cases by a carefully performed aortogram. Aortography provided definitive diagnosis in the patient described in the paragraph above.

Therapy: This will consist of nephrectomy or direct arterial repair for main renal artery thrombosis, and in most cases subtotal resection of the kidney in instances of occlusion of the smaller branches of the main renal artery. When hypertension has resulted from renal ischemia, surgical relief can be expected, as in the case of Wilkey and associates[44].

SUMMARY

Hypertensive diseases are among the commonest that afflict mankind. Patients with pathologic blood pressure elevation fall into two general categories, those where a specific etiology amenable to surgical management can be defined and a second group where either the cause of the blood pressure elevation evades discovery or where the cause lies in disease of the renal parenchyma. Despite progress in the medical management of the latter group, therapy is not characterized by cure. Hypertensive patients are cured and the cardiac, renal, vascular, ocular, and cerebral sequelae of the disease either relieved or prevented only when a specific cause can be discovered and the basis for the hypertension eradicated by operation. Among the commonest of the surgically remedial hypertensive states are those of renovascular origin.

Renal artery stenosis is the commonest cause of the Goldblatt phenomenon with renal A-V fistula, renal arterial aneurysm and renal arterial thrombosesembolism being of distinctly lesser incidence. Patients who should especially be suspected of having this important etiology of their hypertension are considered, with the important concept being that any individual with physiologically important disease and with an altered prognosis should be subjected to diagnostic study. The manner and rationale of work-up and treatment are reviewed with emphasis on the role of angiography and arterial repair respectively. The results of surgical management both in our own group of patients and those reported in the literature have been gratifying.

As knowledge and interest on the part of the physician responsible for the care of the individual hypertensive patient increase, a greater and greater number of patients with "renovascular" disease will be seen. Only then will we realize full benefit of a most important laboratory investigation performed by Goldblatt almost 30 years ago.

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ROLE OF THE KIDNEY IN EXPERIMENTAL HYPERTENSION

David Modai, M.D.*

Richard Bright in 1836 (7), while discussing the pathologic findings associated with diseased kidneys, made the following remarkable statements: "The obvious structural changes in the heart have consisted chiefly of hypertrophy with or without valvular disease . . . This naturally leads us to look for some less local cause, for the unusual efforts to which the heart has been impelled: And the two most ready solutions appear to be either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately: or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant subdivisions of the vascular system." These illuminating observations opened the chapter on the association between the kidney and hypertension. About 60 years later, Tigerstedt and Bergmen ([68]) demonstrated the pressor activity of kidney extracts. They assumed that the activity was due to a vasoconstrictor, which they called "renin".

The experimental production of hypertension by constriction of the renal arteries of dogs, reported in 1934 by Goldblatt et al[22], was the stimulus for an extensive experimental and clinical effort still being very vigorously pursued. Later, when the renin-angiotensin pressor system was independently elucidated by Braun-Menendez et al[6] and Page and Helmer[53], it was felt by many investigators that the key to the problem had been found. However, an enormous amount of experimental and clinical data accumulated since that time indicates that the genesis of hypertension is much more complicated than was initially believed. Despite the achievement of Rittel et al[59] and Bumpus et al[8], each of whom reported the synthesis of angiotensin in 1957, the present status of our knowledge seems far from understanding this problem.

The clinical counterparts of the above experiments should probably be considered to have started with the idea put forward by Ask-Upmark[1] in 1929 that unilateral renal disease might be related to hypertension. The first report on a successful nephrectomy, which was planned to improve hypertension, was published by Butler[9] in 1937. A considerable number of nephrectomies have subsequently been performed with the hope of curing hypertension. However, since they were not usually based on solid criteria, the results were generally unsatisfactory. Smith[64] reviewed 575 nephrectomies published in the literature

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From the Renal and Nutrition Section, Division of Medicine.

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*On leave of absence from Medical Department, Donolo Government Hospital, Jaffa, Israel.

from 1937 to 1956, and concluded that no more than 26% fulfilled the criteria for post-operative cure of hypertension.

Most of the patients, in the early period under consideration, had nephrectomy done for unilateral pyelonephritis. A proportion of these patients had renal ischemia secondary to obstruction of main arteries[12,35,41,43,56,62]. This type of renal involvement, previously considered a rarity, has gradually become recognized as a relatively common disorder associated with high blood pressure.

Experimental Considerations

The exact mechanism associating the diseased kidney with hypertension is not clear. None of the current hypotheses is capable of encompassing all the relevant experimental data. Only part of the possible mechanisms will be discussed below, along with a few of the favorable and unfavorable experimental facts.

Goldblatt Mechanism

Following Goldblatt's experiments a concept has been developed according to which an ischemic kidney secretes a pressor substance, thus causing hypertension.

The response to the Goldblatt operation was shown to vary in different animal species. It was demonstrated that in rabbits[14], rats[75] and other species[25], unlike dogs, constriction of only one renal artery is enough to produce persistent hypertension. Man proved to belong to the more susceptible group of species.

Interruption of nervous pathways from the ischemic kidney at different levels does not prevent the development of hypertension[25], thus implying that a humoral mechanism is probably responsible. This assumption is supported by a number of experimental data: Although constriction of both renal arteries in the dog results in hypertension, the blood pressure of the animal will remain normal if both renal veins are occluded at the same time[25], regardless of the profound uremia which develops. That the hypertensive effect is not related to some interference with renal excretory function was shown by the fact that hypertension can be produced in the dog by a moderate constriction of both renal arteries, which will not be accompanied by any detectable disturbance of the excretory function[11].

In a dog made hypertensive by clamping one renal artery, removal of the clamp or excision of the "clamped" kidney during the first few weeks following the procedure causes almost immediate return of the blood pressure to normal[24]. Byrom and Dodson[10] made rats hypertensive by unilateral nephrectomy and constriction of the artery of the remaining kidney. Removal of the arterial clamp after three months of persistent hypertension resulted in prompt decrease of the blood pressure. These results have been confirmed by Ledingham[42]. Wilson and Byrom[76] showed that if the other kidney is left intact, the blood pressure will remain elevated in many of the animals even after removal of the clamped kidney. They were also able to correlate the level of hypertension following removal of the clamped kidney with the degree of damage found histologically in the unclamped kidney. They suggested that this damage, probably secondary to the high blood pressure to which this "unprotected" kidney had been exposed, is responsible for the residual hypertension.

Houssay et al[33,34] showed that when an "ischemic kidney" from a chronic hypertensive dog is transplanted into the neck of a normal or nephrectomized dog, hypertension ensues, whereas transplantation of a normal kidney did not cause such an effect. However, the interpretation of these experiments was subsequently seriously questioned by Taquini et al[67] who showed that the renin content of the grafted kidneys was initially normal in most cases and increased only after being grafted. In a similar experiment it was subsequently shown by Blalock[3] that whereas hypertension will not appear in a nephrectomized animal into which a normal kidney has been transplanted, the blood pressure will increase if the arterial supply to this kidney is constricted. It will again return to normal upon removal of the constriction. Schlegel et al[61] have removed one kidney of a dog and simultaneously clamped the artery of the remaining one. The resulting persistent hypertension could be relieved by removing part of the remaining kidney, thus presumably alleviating a relative ischemia and rendering the diminished blood supply sufficient for the remnant of renal tissue.

The concept of the renin-angiotensin system can be briefly summarized as follows: The enzyme renin is formed and secreted by the kidney and acts upon renin substrate, which is an α_2 globulin component of the plasma. The resulting product, angiotensin I, is a decapeptide which is physiologically inactive. A second enzyme, the converting enzyme, is needed in order to convert the inactive angiotensin I into the octapeptide, angiotensin II, which is the active vasopressor substance. Various experimental data, summarized by Tobian[72], seem to indicate that the site of renin formation in the kidney is the juxtaglomerular apparatus, and suggest that the specific granules of these cells are the renin. The renin-angiotensin pressor system represents the humoral mediator of hypertension caused by the ischemic kidney, the juxtaglomerular cells acting as regulators of renin secretion by virtue of their sensitiveness, as "stretch receptors"[72], to changes in arterial flow or pressure.

If the above concepts are true, then pressor activity should be detectable in the peripheral and renal venous blood of subjects suffering from hypertension associated with an ischemic kidney. This crucial point is, unfortunately, still under great debate, and especially so in relation to chronic hypertension.

Chronic hypertension refers to one of several months duration, in contrast to the acute stage which in experimental animals usually includes the first few days following the institution of hypertension. This distinction of phases is important since the initiation of hypertension (in the acute phase) and its maintenance (in the chronic stage) might be due to different mechanisms.

Helmer and Judson[32,36,37] using both an aortic strip method and an intact cat preparation, have consistently found increased amounts of "renin" in the renal vein blood of patients with an ischemic kidney and hypertension. Similar findings were obtained by Skeggs et al[63] who measured pre-formed angiotensin in the blood. On the other hand, Braun-Menendez et al[5] were unable to demonstrate increased vasopressor activity in the blood of chronic hypertensive rats. Peart[54] studied the renin content of renal vein plasma of rabbits made hypertensive by unilateral nephrectomy and constriction of the remaining renal artery. At no stage of the hypertension was he able to detect the presence of renin. However, when renin was infused into the renal vein close to the kidney and the blood pressure of the animal increased, renin was readily demonstrable in blood collected from the renal vein distal to the site of renin infusion.

An indirect approach to the same problem was described by Blaquier et al[4] who used the technique of isovolemic cross circulation in rats. Whereas pressor activity of renin or angiotensin II amide infused into the donor was readily detectable in the recipient, no such activity was found when the donor was a rat with renal hypertension of one week's duration. Omae et al[51] measured the release of pressor substances with a preparation employing kidney grafts of rats. They found that the activity of the kidney graft depended on the method used to render the donor animal hypertensive. Whereas kidneys subject to perinephritis or infarction liberated little or no renin, kidneys whose artery had been compressed, released slightly greater than normal amounts of pressor substances. This could mean that the mechanism of production of hypertension is not the same in the different studies cited, or that the renin system does not play a role in either of the cases reported.

Another aspect of the problem under investigation is concerned with the renin content of the kidneys. It was shown[65] that during the acute phase of hypertension following constriction of the renal artery in the dog, there was a rapid increase in the renin content of the ischemic organ. Although the blood pressure remained elevated, the increase in renin was transient and usually returned to normal within a few days. The renin content of the ischemic kidney remains persistently normal in chronic hypertensive dogs[66]. In the acute phase of hypertension in the rat, while renin in the ischemic kidney increases, it disappears from the opposite kidney[29]. Haas and Goldblatt[30] have reported that under similar conditions in the dog, the sum of renin found in both kidneys is increased compared to normal kidneys. On the other hand, Regoli et al[58] have demonstrated a marked discrepancy between the kidney renin content and hypertension. In a rat, after unilateral nephrectomy, if the artery of the remaining kidney is clamped, hypertension develops without any increase in the renin content of the kidney. As already stated[29] the "clamped" kidney acquires a high renin content. However, after removal of the "unclamped" kidney, the renin content of the remaining one decreased to normal within a few weeks. At the same time the blood pressure remained high.

A brief note concerning the relationship between the kidneys and adrenal glands seems appropriate here. Goldblatt[23] has shown that bilateral adrenalectomy abolishes the development of hypertension following renal artery constriction. Removal of the medulla alone had no such effect. It was subsequently demonstrated that the width of the zona glomerulosa of the rat adrenals, which is the site of aldosterone formation, is increased following administration of renin[13]. Moreover, although hemorrhage in normal dogs stimulates aldosterone secretion, this effect was prevented in nephrectomized animals[50]. Nephrectomy also lowers the basal secretion of aldosterone in the dog. Laragh et al[45] and Genest et al[21] have demonstrated that synthetic angiotensin is a potent stimulus to aldosterone secretion in man. Bilateral adrenalectomy has been shown to be associated with a striking accumulation of granules in the juxtaglomerular cells[15]. This phenomenon could be prevented by injections of DCA. The state of hypergranularity in these cells is believed by many to represent active secretion. The above inhibition of granularity also followed administration of aldosterone to animals consuming a diet of average or high sodium content[71]. At the same time a decrease in the renin content of the kidneys was found. Thus it seems reasonable to conclude that an inverse relationship exists, possibly as part of a feedback system, between the mineralocorticoid hormones and the state of activity of the juxtaglomerular apparatus. The latter would respond directly to the hormone level in the blood[16], or alternatively, the inhibitory effect of the mineralocorticoids would be mediated through salt metabolism[31]. In this regard it is interesting to note that a number of cases were reported in which a clinical and metabolic picture of primary aldosteronism was present, presumably secondary to renal ischemia[26a] and on several occasions both hypertension and aldosteronism were cured by removing the ischemic kidney.

To what extent, if any, excess aldosterone is responsible for the elevated blood pressure in renal ischemic hypertension is a problem that needs much more investigation.

Renoprival Hypertension

Grollman et al[27] showed that in the rat complete nephrectomy was followed by the development of hypertension, which would persist as long as the animal lived. The same phenomenon was demonstrated in the dog; when the excretory function was maintained artificially by dialysis, hypertension still supervened[28]. Muirhead et al[46] showed that a kidney homograft restored the renoprival hypertension in the dog to normal levels. The same effect was subsequently obtained by grafting renal medulla alone[47]. It was thus shown that maintenance of normal blood pressure in the experimental conditions studied was related to some non-excretory function of the normal kidney. It was assumed that in the dog the hypertension which follows both renal artery constriction and total nephrectomy is caused by a single mechanism, namely, inhibition of the vaso-depressor activity of the normal kidney.

The above assumption is also consistent with the following observations: Pickering[57] made rabbits hypertensive by removing one kidney and constricting the artery of the remaining one. Removal of the kidney seven to fifteen weeks after constricting the artery did not affect the hypertension which persisted until the animal's death. However, if the clip was removed from the artery of the sole remaining kidney during the same stage of chronic hypertension, the blood pressure returned to normal[2].

The exact nature of the mechanism involved still awaits clarification; does the normal kidney excrete a vaso-depressor substance, or, alternatively, is it capable of inactivating some vasopressor factor elaborated elsewhere in the body? Muirhead et al[48] obtained a crude extract of renal medulla which was capable of preventing the development of hypertension in renoprival dogs eating a high sodium and protein diet. The same extract inhibited the development of the renoprival pattern of hypertension in animals given daily menin injections[49]. These facts led them to conclude that the protective effect of renal medullary extract is not related to the renin-angiotensin system, and might probably be due to an effect on small arteries and arterioles.

Pressor-Depressor Hypothesis

It has been suggested that the kidney is capable of exerting two opposite types of vasoactive functions: One is vasopressor, probably mediated through the renin-angiotensin system. This would cause the hypertension appearing immediately following constriction of the renal artery and would also be responsible for maintaining the elevated blood pressure during the acute phase only, after constriction. The second function is vaso-depressor, acting indirectly by counteracting a pressor mechanism which is extra-renal in origin. It might be identical with Muirhead's medullary principle mentioned above. In addition, the renal vaso-pressor principle, when secreted in minute amounts, which in themselves are too small to produce a detectable vaso-activity, is able to inhibit the vaso-depressor function of both kidneys, and consequently the blood pressure will rise.

Wakerlin et al[73] were the first to produce antirenin antibodies by repeated injections of hog renin into dogs. The antibodies were considered to be quite specific, and this procedure was subsequently shown[74] to be effective in reducing experimental renal hypertension in the dog. Moreover, the antirenin titer in the animal's blood correlated with its anti-hypertensive effect. Similar results have recently been reported in monkeys[18a]. Kolff and Page[38] have also demonstrated that antirenin diminished or abolished the hypertensive response to injected renin. In addition, the pressor response to constriction of the arteries of transplanted kidneys in bilaterally nephrectomized dogs was also diminished by antirenin. However, the development of renoprival hypertension in the dog was not affected by antirenin, nor could antirenin modify the already established renoprival hypertension. These results do not agree with the concept mentioned above, that both the renal and renoprival varieties of hypertension share a common underlying mechanism, namely, inactivation or elimination of the anti-hypertensive function of the normal kidney. If this concept were correct, one would expect both varieties of hypertension to respond to antirenin in the same fashion. In fact, antirenin should have no effect on hypertension in any of them. Kolff and Page, therefore, made the assumption that renin is capable of inhibiting the anti-hypertensive function of the normal kidney. Inhibition of this normal vaso-depressor activity, and consequently appearance of hypertension, might therefore be produced either by total nephrectomy or by renin secreted as a result of renal artery constriction.

Floyer[18] arrived at a similar hypothesis based on a series of experiments. He produced hypertension in rats using the following procedures: (a) unilateral nephrectomy and clamping the artery of the remaining kidney. (b) bilateral nephrectomy. Group (a) responded with a prompt development of hypertension; whereas renoprival hypertension in group (b) appeared characteristically after a delay of three days or more. On subsequent removal of the remaining kidney in group (a) hypertension persisted without any significant decrease. This result could not be attributed to renoprival hypertension following the renal ischemic variety, since the characteristic delay of three days was absent.

The Role of Electrolytes in Hypertension

As mentioned previously Goldblatt[23] has shown that complete removal of the adrenal cortex interfered with the development of hypertension following constriction of the renal artery in the dog. It was subsequently demonstrated by Floyer[17] that adrenalectomy also prevents the appearance of renoprival hypertension. This inhibiting effect of adrenalectomy, however, could be prevented in both varieties of hypertension by administration of salt to the animal[17,52]. It could be seen that the adrenal cortex plays an important role in the extra-renal pressor mechanism and that a high sodium intake can replace a functioning adrenal cortex in the maintenance of renal and renoprival hypertension.

Different kinds of experimental hypertension are aggravated by an excessive salt intake. Kolff and Page[39] have shown in renoprival animals that the blood pressure will go much higher in those animals given excess salt and water. This effect is probably not due to overhydration per se. A similar effect was observed in the case of DOCA hypertension, more hypertension being produced by adding salt to the animal[55]. Moreover, Meenley et al[44] have studied normal rats given normal diets which varied only in their salt content. After twelve months they found that the blood pressure of the animals increased in a stepwise fashion which correlated with the amounts of sodium added to their diets.

There is also evidence that other ions, especially potassium, may play an important role in the causation, maintenance and severity of different types of experimental hypertension. Meneely et al[45] have reported that in rats made hypertensive by excess salt much of the hypertension could be prevented by simultaneous high potassium intake. On the other hand, Friedman et al[20] showed that in rats made hypertensive by renal ischemia a low potassium intake was followed by a drop of blood pressure to near normal levels. Rosenman et al[60] observed that potassium deficiency prevented a rise in blood pressure during DOCA administration. A similar effect in normotensive rats has been reported by Freed and Friedman[19]. When these rats were maintained on a potassium deficient diet, there was a marked reduction in blood pressure, and, interestingly enough, rats given a similar diet which was also deficient in sodium did not manifest any reduction in blood pressure.

An interesting observation relating the salt intake to the reactivity of blood vessels was made by Zsoster et al[77]. They placed groups of rats on diets of either low, normal or high salt content. After three months they tested the sensitivity of the mesoappendix blood vessels of the animals to norepinephrin. A progressive increase in sensitivity was found, and was directly related to the increasing sodium content of the diet. Moreover, the sensitivity of the vessels increased in all groups after infusion of isotonic saline. The latter effect, however, was greatest in the animals maintained on a low sodium diet.

The electrolyte composition of the vessel walls in hypertensive and normotensive states was studied by Tobian. Tobian and Redleaf[70] compared the electrolyte composition of the aortic wall of rats made hypertensive by three different procedures with control groups undergoing the same procedures which did not become hypertensive. In all three hypertensive groups they found increased amounts of potassium and also of sodium in the vessel wall. They believe that the results reflect intracellular rather than extracellular increase of these electrolytes. A similar result was obtained in rats made hypertensive by renal ischemia[69], and the intracellular magnesium, phosphorus and water content was also found to be increased. In the same animals it was demonstrated that these changes were not related to nitrogen retention. Redleaf and Tobian[58] subsequently studied the effect of antihypertensive treatment on aortic wall composition. They found that when hypertensive rats were treated with reserpine and a marked drop in blood pressure occurred, it was accompanied by a simultaneous drop in the potassium content of their aortic wall.

Tobian makes the assumption that "something related to the hypertensive state either changes the cell membrane of the arterial muscle cells or changes the number of binding sites on the intracellular proteins (or both) to produce this electrolyte pattern." He further speculates that similar compositional changes occur in the walls of the arterioles. These changes could affect the level of blood pressure through one of the following mechanisms: (1) Intracellular accumulation of water and electrolytes would cause swelling of the cells and consequently the arteriolar lumen would narrow. This would bring about increased resistance and elevation of blood pressure. (2) Any deviation from the "optimal" ionic composition would affect the molecular kinetics of actomyosin and cause shortening of the vascular muscle fibers. (3) Increased intracellular electrolyte concentration would cause changes in the membrane potential. This, in turn, would alter the sensitivity of arteriolar muscle to endogenous vasoactive substances.

COMMENTS

An attempt has been made to outline some of the available data and ideas related to the role of the kidney in experimental hypertension. The purpose has been to point out some problems, difficulties and controversy of ideas still prevailing in this field, rather than to present or prefer any firm concept. Many of the individual problems in the field are difficult to solve because of technical reasons, like the one involved in determination of pressor activity in blood and tissues. Others are related to variations in susceptibility, and perhaps in physiologic responses between different animal species. Different experimental conditions constitute another series of obstacles to our understanding of the mechanisms involved. However, the greatest difficulty is probably our lack of knowledge concerning the existance of many other factors which play a role in the genesis of hypertension, and their complex and variable interrelationship.

In the face of such an uncertain experimental background it seems surprising that a relatively large proportion of patients have been apparently cured or improved by either removing or "revascularising" ischemic kidneys. In approaching other renal diseases which are sometimes associated with hypertension, our understanding of the underlying mechanisms is even poorer than in the case of ischemic kidneys.

The issue is even more obscure in dealin with so called human "essential hypertension." A demonstration of the state of complete dissociation of opinions and concepts is illustrated in the following two quotations: Homer W. Smith[64] says, "The kidney appears to be the victim and not the culprit in this disease": On the other hand H. Goldblatt[26] believes that "The primary cause of essential hypertension in man is intrarenal obliterative vascular disease from any cause, usually arterial and arteriolar sclerosis."

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THE VARIEGATED SPECTRUM OF THE PHEOCHROMOCYTOMA

David Baldwin, M.D.

Sir Arthur Conan Doyle[1] has expressly stated that the prime factor responsible for the indisputable success of the late Professor Moriarty, arch-criminal, and supreme antagonist of Holmes, the bee-keeper, was the concealment of his power to affect his environment adversely. Of equal talent in the lore of clinical medicine is the pheochromocytoma which can simulate a host of disorders within its clinical spectrum, yet remain unsuspected.

The usual patient with a pheochromocytoma as described in numerous sources[2,3,4] is of thin body build, is of any age, and suffers from paroxysmal or sustained hypertension. The paroxysmal episodes are usually associated with headache, nervousness, dyspnea, abdominal or chest pain, and accompanied at times by nausea and vomiting. Frequently such patients suffer marked sweating, peripheral vasoconstriction, and lacrimation during attacks, and may develop convulsive seizures. An attack may be precipitated by massaging the costovertebral angles, or by palpation of such a tumor through the abdomen. Chronically they may develop diabetes mellitus with polyuria, polydipsia, and glycosuria; and frequently they develop an elevated basal metabolic rate.

In ten percent of cases the tumors are multiple[4]; in ten percent they are located in extra-adrenal para-aortic chromaffin tissue; and in three[4] to ten percent[2] they are malignant. Frequently they are familial, occurring in many members of a family[4], "probably inherited in dominant genetic fashion."[5]

Because this tumor secretes epinephrine and norepinephrine and their metabolites: metanephrine, normetanephrine and 3-methoxy-4-hydroxy-mandelic acid (or vanillylmandelic acid)[3], definitive tests for these substances in blood or urine[6,11] have been extensively utilized to detect its presence.

Additional laboratory procedures for diagnosis and screening include the use of drugs to provoke hypertension in normotensive patients in whom the diagnosis is suspected. These include the subcutaneous administration of histamine[12], of mecholyl[13], and the intravenous administration of tetraethyl-ammonium chloride[14] (or bromide)[15]. These have been used alone, or in combination with measurements of plasma[16,17] or urinary catecholamines. Adrenolytic drugs including phentolamine, piperoxan, di-

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benamine, and priscoline have also been useful as diagnostic adjuncts in hypertensive patients suffering from this disorder; and the values, limitations, and pitfalls of all of these tests have been the subject of many reports[18,23].

The purpose of this review is to attempt, through an analysis of the pathophysiology of the catecholamines, to derive a clearer understanding of the multiple and bizarre clinical forms that chromaffin, catecholamine-secreting, tumors may adopt. Many indeed are the "masks of the pheochromocytoma." These "masks" are sketched in this review.

The Mask of Diabetes

The association of diabetes mellitus with tumors of the adrenal medulla has long been recognized[2]. Yet the symptoms of diabetes in many instances have dominated the clinical picture to such a degree that the underlying diagnosis has been obscured. Such instances are well exemplified by the case reported by Griessmann[24] of a patient who presented initially in diabetic coma, yet whose glucose tolerance became normal after the removal of a pheochromocytoma. Hutchison[19] reported a case who was considered to suffer from diabetes and "insulin reactions," before the correct diagnosis was finally made. Desjardins[25] described a diabetic patient with a pheochromocytoma who after surgery developed severe diabetic retinopathy which persisted for six weeks.

Approximately 60 percent of pheochromocytomas are associated with fasting blood sugars greater than 120 mg.%; and in 25 to 40 percent of cases, the glucose tolerance test is clearly in the diabetic range[26]. In most instances the manifestations of diabetes mellitus, including polyuria, polydipsia, glycosuria, and abnormal glucose tolerance disappear after removal of the tumor[25,27]. In a few patients however the diabetes has persisted[28,29].

It has long been known that epinephrine stimulates hepatic glycogenolysis with release of glucose from the liver by acting on hepatic cell membranes to release activators of a phosphorylase necessary for the degradation of glycogen to glucose[3]. Epinephrine also acts peripherally to block the disappearance of glucose from the blood. The latter action has been recently documented by Fritz[30] in the eviscerated, insulinized dog in which epinephrine increased plasma glucose concentration above control values whether the blood levels prior to epinephrine infusion were normoglycemic or hyperglycemic.

Despite the evidence that epinephrine can produce hyperglycemia, causal understanding of the impairment of carbohydrate metabolism manifested by patients with pheochromocytomas is not clearly understood. In view of the episodic nature of epinephrine-induced hyperglycemia, *chronic* impairment of glucose metabolism requires further interpretation. DeVries[27], and Ricketts[3] have suggested that the islet cells of the pancreas may become exhausted in the face of prolonged or repeated epinephrine-induced hyperglycemia. Ricketts[3] has also speculated that "certain 11-17-oxysteroids secreted in excess by the adrenal cortex in response to hyperephinephrinemia may have an additional effect on islet cell function." Yet at the present time a definitive explanation of this extra-pancreatic variety of diabetes is not available.

The Mask of Thyrotoxicosis

Not infrequently the diagnosis in patients with this tumor is mistaken for thyrotoxicosis. These two disorders have many features in common. Both entities are associated at times with symptoms of palpitation of the heart, tremor, excessive perspiration, heat intolerance, and weight loss in the absence of anorexia. They also suffer from weakness and easy fatiguability, and sometimes run a low grade fever. In many instances the basal metabolic rate is elevated[2,31]. Some patients suffering from pheochromocytomas have developed paroxysmal swelling of the neck; and a very few may have enlargement of the thyroid gland[32].

Despite the elevation of the basal metabolic rate, more definitive studies of thyroid function have almost consistently been normal. An exception is the recent report[31] of an unusual patient in whom an elevated basal metabolic rate was also accompanied by a markedly elevated 24-hour I^{131} thyroidal uptake of 67% (with a conversion ratio of 69%). Other thyroid function studies in this patient were normal. Six months after surgical removal of a pheochromocytoma the radio-iodine thyroidal uptake had fallen to normal values.

Interrelationships of the thyroid and the adrenal medulla have been studied for many years. There is abundant evidence that thyroxin potentiates the metabolic effect of the catecholamines. The rise of blood pressure induced by epinephrine is markedly reduced in animals and in man following thyroidectomy, and increased in thyrotoxicosis[33,35]. Furthermore Brewster[36] has demonstrated in dogs that the calorigenic effect of norepinephrine and epinephrine were markedly augmented by thyroid feeding; and thyroid also potentiated the effect of the catecholamines on heart rate, cardiac index, and ventricular stroke work per unit of filling pressure. In these hemodynamic effects norepinephrine appeared to play the more significant role. Also Swanson[37] has demonstrated in rats that thyroidectomy inhibited (and that thyroxin potentiated) the calorigenic effect of adrenalin in direct proportion to the amount of thyroid hormone employed.

A converse effect of the catecholamines upon thyroxin has also been described. Brewster[36] demonstrated in dogs that the calorigenic and hemodynamic effects of thyroxin could be abolished by an epidural, sympathetic block which obliterated the reflex release of the catecholamines.

Whether there exists a direct action of the catecholamines upon the thyroid gland is not clear. Ackerman[38] has demonstrated in normal and hypophysectomized dogs an increased release of thyroxin and triiodothyronine in thyroid venous blood after intravenous epinephrine and norepinephrine, indicating such an action. On the other hand, other authors favor the view that epinephrine acts by increasing peripheral utilization of thyroxin. Eskelson[39] demonstrated a fall in serum protein bound iodine after epinephrine injection in rats, and ascribed this to increased peripheral utilization. Botkin and Jensen[40] found in rats that epinephrine injection was followed not only by a decreased serum protein bound I^{131} concentration but also by a decreased content of I^{131} in the thyroid gland. Consequently they postulated that increased peripheral utilization of thyroxin was associated with an increased secretion of thyrotropin from the pituitary, and with an increased thyroxin turnover. Such an interpretation is compatible with Soffer's[41] presumptive demonstration by bioassay of increased circulating thyrotropin (over control values) in thyroidectomized dogs given adrenalin in oil.

Whatever the precise, mutually-potentiating mechanisms, or the direct or indirect relationships involved, thyroid-catecholamine interaction has profound clinical and therapeutic significance. The amelioration of thyrotoxic symptoms by sympatholytic agents is now well documented in hyperthyroid patients,[42] and in normal subjects with thyrotoxic symptoms induced by thyroid hormone medication[43]. Conversely it is a consistent clinical observation that resection of a pheochromocytoma eliminates the "thyrotoxic-like" symptoms associated with this tumor. Certainly it is hardly surprising that the dynamic interrelationships between the catecholamines and thyroid hormones make differential diagnosis between disorders of these glands in many instances perplexing.

The Mask of the Gastro-intestinal Disorder

Fifteen percent of patients with pheochromocytoma in one series,[44] and thirty-three percent in another[45] have presented with abdominal symptoms suggesting a wide variety of gastro-intestinal disorders. Indeed in some patients suffering from this disease severe abdominal pain may be the *primary* presenting complaint[46]. In one patient[46] the pain was episodic and recurred over a period of four months. Its epigastric location and its association with severe nausea and vomiting, had led to a misdiagnosis (as in other patients) of a peptic ulcer, although as usual in this disease fluoroscopic examination of the gastro-intestinal tract had been negative.

Kvale,[47] Richmond,[48] Gendel,[49] Miles,[45] and Rosch[50] each reported cases in which actual gastro-intestinal bleeding was present. In view of these patients and others, Talbot[51] has stated that repeated instances of gastro-intestinal bleeding may be a significant feature of the clinical course of patients suffering from this tumor, although bleeding episodes and hypertension may not coincide[49].

Upper abdominal pain coupled with marked weight loss[32] can readily suggest the diagnosis of gastric malignancy. One of Miles' cases[45] with severe epigastric pain only moderately relieved by alkali, repeatedly passed tarry stools. Two fruitless laparotomies were performed before the patient finally died. Horn[52] described a patient whose paroxysmal hypertension was triggered by severe upper abdominal discomfort following eating, and in whom the diagnosis was only suspected when it was noticed that the bloating was at times accompanied by sudden hypertension, particularly when he lay on his left side. Indeed in Graham's[53] series of 207, cases in approximately two percent, attacks of hypertension followed eating. By contrast Pincoff's[54] patient suffered from attacks of paroxysmal hypertension which terminated with protracted vomiting. These bizarre associations have made the correct diagnosis profoundly perplexing.

In some instances perhaps, abdominal distress may be causally ascribed to intestinal hyperperistalsis[44] induced by excessive circulating catecholamines. In other instances abdominal pain is directly the result of local compression of neighboring tissue by extension of the tumor. This was presumably the cause in some of the cases surveyed by Thorn[44]. Another possible explanation may be excessive distension of the bowel[55] inasmuch as prolonged infusions of noradrenaline will produce marked dilatation of the colon experimentally in rabbits[56].

Probably the major explanation for abdominal pain is the profound vasoconstrictive effect of the catacholamines on the arterioles of the small bowel. Autopsy studies of dogs given prolonged norepinephrine infusions have revealed mucosal ulcerations, submucosal hemorrhages, necrosis of the mucous membrane throughout the entire gastro-intestinal tract, and even patchy areas of gangrene of the intestinal wall[59,58]. Similar pathological findings were reported by Brown[55,59] in three patients with pheochromocytomas who died with multiple minute ulcerations and perforations of the bowel accompanied by diffuse proliferative arteritis in the intestinal wall. Of note is that fact that these lesions were unaccompanied by thrombotic occlusion of any major mesenteric vessels. Brown[59] and Rosch[50] described similar findings in patients who were intensively treated with vasopressor substances for hypotension accompanying myocardial infarctions. Gastro-intestinal lesions of this nature have predictably obscured the underlying diagnosis in the majority of instances.

The Mask of the Psychiatric or Neurological Disorder

It is not unexpected that a disorder characterized by hormonal disturbances of the autonomic nervous system might present with a multiplicity of vasomotor phenomena. That psychiatric abnormalities may be associated with this disorder is not as well recognized. Yet toxic-delirious reactions have been reported by Vaquez[60], manic episodes by Snyder[61], delusional-hallucinatory reactions by Barker[62], psychotic episodes associated with loss of consciousness by Spalding[63]; and "inward excitement without reason" has been analyzed psychoanalytically by

Kasanin[64]. Severe anxiety has been the dominant complaint of patients with catecholamine-hypertension; and two patients reported by Doust[65] sought medical advice for this symptom primarily.

Many instances of convulsive episodes associated with pheochromocytomas have been reported: and in certain patients the seizures occur predominantly at night.[19,32,66,67] Electroencephalographic studies of these patients however, have provided little diagnostic assistance. In Guarneri's[68] case the EEG revealed an "atypical record consistent with a mild form of epileptic dysrhythmia with no localized abnormality." Bruce[69] reported "bursts of high voltage of three second activity in all leads" plus "transient right parietal focal signs." In another patient there were mild electroencephalographic slow wave abnormalities which disappeared after resection of the tumor.

Neurological complications of paroxysmal hypertensive seizures are legion. Intracerebral hemorrhages have been reported in the cortex, pons, cerebral peduncles, ventricles, cerebellum, and subarachnoid space.[67] Moreover a pheochromocytoma was the underlying diagnosis in one patient who presented initially as a "meningitis with coma."[70] Vascular lesions in the central nervous system may account for many of the bizarre manifestations of this disorder.

The Mask of the Neuro-Cutaneous Syndrome

The relationship of the neuro-cutaneous syndrome to the pheochromocytoma has been stressed repeatedly by many authors.[71,72] Of the four interrelated neuro-cutaneous syndromes Glushien[71] has documented an association of this tumor with multiple neurofibromatosis, and with von Hippel-Lindau's disease (angiomatosis retinae et cerebelli). In addition, in our hospital two cases have been described at autopsy in which pheochromocytomas were accompanied by cystic astrocytomas of the brain.[73] No evidence has as yet been found to link this disorder with the other two neuro-cutaneous syndromes: tuberous sclerosis, and Sturge-Weber's syndrome (encephalotrigeminal angiomatosis). Ten to twenty percent of patients with pheochromocytomes had one of these first two neuro-cutaneous syndromes: and thirteen percent of patients with neurofibromatosis have been proven to have pheochromocytomas.

Other associated features include long, slender hyperextensible fingers, hyperextensible knees, and in several instances dorsal kyphoscoliosis of the spine. Of diagnostic significance are those instances in which a forme fruste of the neurofibromatosis syndrome is present. One of the cases described by Glushien had only cutaneous pigmentation; and pheochromocytomas have been suspected and diagnosed in patients who had only ocular manifestations of the neuro-cutaneous syndromes. The latter include angiomatosis retinae, neurofibromata of the eyelids, myelinated corneal nerve fibers,[74] and phakomas of the retina.[75] Of interest is the unusual case of neurofibromatosis of the intercostal nerves. Here the radiological finding of notching of the ribs in the absence of coarctation of the aorta in a patient with hypertension should lead the clinician to rule out the possibility of a pheochromocytoma.[3]

The Mask of Heart Disease

Probably the most insidious of all the the systemic disorders induced by excessive secretion of the catecholamines is heart disease. Patients with pheochromocytomas may present with attacks of severe angina,[2] or even with acute pulmonary edema in the absence of previous cardiac enlargement.[76] They may develop a painless myocardial infarction,[77] may present (particularly during paroxysmal hypertension) with practically the entire gamut of cardiac arrhythmias;[76] and pheochromocytomas may produce sudden death from cardiac standstill.[78] These manifestations of the of the pharmacological actions of the catecholamines have been studied both in normal subjects and in the experimental animal.

Raab[78] postulated many years ago that norepinephrine and epinephrine were major contributing factors underlying the genesis of many varieties of heart disease. It was his view that the catecholamines intensify oxygen consumption by myocardial tissue and decrease the conversion of oxygen-energy to mechanical work. The catecholamines may also produce local myocardial hypoxia, favor myocardial hypertrophy, elevate the systemic blood pressure and are presumed to cause hyperplasia of arterial intima.[79] Circulating catecholamines are extensively absorbed and stored in the heart where they increase anaerobic glycolysis within the myocardium.[80]

Supportive evidence for some of these postulates may be found in the literature. L-norepinephrine myocarditis has been documented convincingly in the heart muscle of dogs receiving prolonged infusions of norepinephrine,[58,81,82] in which diffuse focal necrosis, inflammatory exudates, and numerous subepicardial and subpericardial hemorrhages are found. In addition, prolonged catecholamine infusions increase the content of total fat and triglycerides in the myocardium, and produce acute elevations in the glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, and alkaline phosphatase content of the dog's serum.[83]

Of profound significance is the observation that seventeen patients under the age of 55 dying of pheochromocytoma-induced hypertension, (paroxysmal or sustained) had myocardial lesions deemed identical to those produced in the dog.[58] Furthermore, similar findings were reported in patients treated intensively with norarterenol for other cardiac disorders. The clinician must be alerted therefore to suspect myocardial damage in the presence of this tumor.

That the heart rate is profoundly altered during the paroxysmal hypertensive episodes of these patients is not unexpected. A study of the effects of epinephrine and norepinephrine in normal subjects[84] has revealed that cardiac arrythmias were frequent. These included atrial ectopic rhythms, atrioventricular block, sinus node block, and A-V nodal and ventricular ectopic rhythms. Arrythmias following norepinephrine administration appeared only at hypertensive levels when the pulse rate was slow; whereas ectopic rhythms following epinephrine infusions appeared regardless of blood pressure or pulse.

Raab[79] has speculated that catecholamine toxicity to the heart derives not only from hypersecretion, as in patients with chromaffin tumors or chronically hyperemotional subjects, but also by "deficient sympatho-inhibitory mechanisms." Another hypothesis includes an increased sensitization of the heart muscle to the catecholamines from excessive adrenal corticoid secretion. According to Raab, the walls of the coronary and peripheral arterioles may also be made vulnerable to catecholamine toxicity by excessive secretion of adrenal mineralocorticoids; and finally, catecholamine toxicity to the heart may be potentiated by thyroxin.[36] Experimental evidence to strengthen the last concept has been described in this report.

The Mask of Kidney Disease

Paroxysmal hypertension may present with anuria, oliguria, azotemia and renal failure.[2] Indeed Carpenter reported a case in which acute tubular necrosis with renal shutdown was the primary clinical feature.[85] In the usual case however, the clinical course of a paroxysm closely resembles rapidly developing malignant hypertension; and urinalysis has been non-diagnostic, revealing proteinuria and cylindruria.

Postmortem studies have revealed renal lesions typical of hypertensive arteriolonephrosclerosis.[86] However, renal biopsies obtained during the operative removal of chromaffin tumors have shown, in addition, hypertrophy and hyperemia of the glomeruli.[87]

The Mask of Bladder Disease

At least twelve patients have now been reported that suffered from chromaffinomas of the bladder wall.[88,91] Such patients complain of intermittent hematuria and paroxysmal vasomotor phenomena upon micturition. These include severe headaches, sweating and syncope. In some of these patients, x-ray cystograms revealed a filling defect. In one, however, only clinical suspicion and an increased excretion of 24-hour urinary catecholamines led to a laparotomy, and removal of a walnut-sized tumor from the bladder wall. All other clinical studies including bladder x-rays had been normal.

The Exceptional Masks

Patients have been reported with Addison's disease[76] owing to invasion of the adrenal cortex by adrenal medullary tumors; and others with added symptoms of hypercorticalism due to coexistent adrenal hyperplasia.[92] Familial and malignant pheochromocytomas of the organs of Zuckerkandl have been reported.[93] These chromaffin cells adjacent to the aorta usually disappear after infancy. One case report even alleges an association of pheochromocytomas with thyroid cancer.[94]

Recently a patient was reported with polycythemia and thrombocythemia in whom an underlying pheochromocytoma was found to contain large stores of erythropoietin. Removal of the tumor was followed by a rapid return to normal values of the red cell and platelet counts.[95]

Patients with pheochromocytoma have been described where the predominant clinical feature was peripheral vascular disease. Here the prominent features of the hypertensive paroxysms were painful, dusky discoloration of single toes, sensations of heat in the feet, abnormal redness of toes and fingers, or absent posterior tibial pulses with decreased oscillometric readings in the legs.[32]

The erroneous diagnosis of toxemia of pregnancy and eclampsia have frequently been made in pregnant patients with unsuspected chromaffin tumors.[96]

Finally, the most outrageous of all case reports of this tumor can be utilized to add final emphasis to the theme of this review. Richmond[48] has recently described the clinical course of a patient who suffered not from paroxysmal hypertension but from *paroxysmal shock*. Epinephrine, unlike norepinephrine, is a vasodilator and may produce hypotension following an initial hypertensive phase.[97,98] Rarely the catecholamine secretion from a pheochromocytoma may be predominently composed of epinephrine instead of norepinephrine. Thus in this patient a rise in blood pressure was followed by profound hypotension. Only after myriad hospitalizations and myriad diagnostic procedures was a paroxysmal episode caught at the very inception of its course when the hypertensive component was revealed. Only then was this most deceptive of all clinical entities considered, properly tested for, and successfully treated.

SUMMARY

In summary, the wide clinical spectrum presented by patients suffering from chromaffin catecholamine-secreting tumors has been presented. Many pathophysiological aspects of this tumor have been discussed; and the interrelationships of the catecholamines with other organ systems described. Many are the "masks" of the pheochromocytoma, including the mask of diabetes, the mask of thyrotoxicosis, of the gastro-intestinal disorder, of the psychiatric, or neurological disorder, of the neurocutaneous syndrome, of heart disease, kidney disease, bladder disease, adrenal cortical disease, hematological disease, and peripheral vascular disease. These variegated bizarre forms make a high index of suspicion vital for accurate diagnosis of this entity.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Trauma to the Arteriosclerotic Limb. G. De Takats, and E. F. Fowler. *Trauma, 47–48 April, 1963.*

The problem of the injured arteriosclerotic limb has been discussed. No attempt has been made to describe the obvious injuries to major arterial pathways. Emphasis was placed on the vulnerability of the arteriosclerotic vascular tree, which responds to minor injuries with a major reaction. The causes of such a vulnerability have been dealt with, together with the methods of study, the natural course of the disease as influenced by the injury and the effect of treatment on the results of the injury. Independent, unbiased medical testimony can establish on objective grounds, the possible influence of trauma on pre-existing peripheral arteriosclerosis.

Metabolic and Nutritional Factors in Peripheral Vascular Disease. G. M. Hass, *International Academy of Pathology Monograph No. 4, Chapt. 8, The Peripheral Blood Vessels.*

This article is concerned with the role of lipids and arterial lipoidosis potentials in the pathogenesis of atherosclerosis. It includes a discussion of physiologic aspects of preparation of dietary lipids for intestinal absorption and the role of absorption of these lipids in the pathogenesis of disease. The significance of intravascular lipid transport and especially of interstitial lipid transport is emphasized. The dependence of the development of the disease on factors which control interstitial mesenchymal reactions is singled out as the most important localization mechanism. These reactions, in turn, are partially linked to those which regulate the systemic metabolism of the lipids. Medial calcific degeneration of arteries with local activation of mesenchyme is a most important factor in the occurrence and localization of atheromatous disease. Combinations of hyperlipemic hypercholesterolemic and medial calcific degeneration with secondary mesenchymal activation are the only means by which a vascular disease resembling human atheroarteriosclerosis can be produced in animals at blood lipid levels corresponding to those which occur customarily in man.

Splenosis: A Sequel to Traumatic Rupture of the Spleen. C. Davis, Jr., R. W. Alexander, and H. D. DeYoung, M.D., *Archives of Surgery 86, pp.523–524, April, 1963.*

Splenosis, the autotransplantation of splenic tissue following severe injury to the spleen, is rarely observed. The clinical features and pathology of splenosis are discussed. The history, clinical findings, and surgical treatment of three children with splenosis are described.

The diagnosis of splenosis should be considered in any case of acute injury to the spleen and/or splenectomy. Multiple intraperitoneal splenic implants following trauma to the spleen may be found incidentally at reoperation or at necropsy.

Splenic autotransplants should not be confused with accessory spleens. These nodules of splenic tissue are grossly and microscopically characteristic of the normal spleen. Splenosis, in conjunction with postoperative adhesions, should be considered in the etiology of acute intestinal obstruction.

The occurrence of splenosis may be related to the technique of splenectomy for either traumatic rupture or medical disease of the spleen.

Prognosis In Infantile Hydrocephalus, Past and Present. D. Yashon. *Journal of Neurosurgery. Volume XX No. 2, pp. 105–111, February, 1963.*

In the history of the treatment of hydrocephalus, many procedures have gained temporary acceptance accompanied by good prognostic reports, only to be abandoned later. In the present series of 147 patients with infantile hydrocephalus, 58 were not operated on. "Arrest" of hydrocephalus is considered present in 31 who are still alive: 13 were considered to have "arrest" at the time of the first examination. A variety of operations was done in 69 patients of whom 29 are still alive. Ventriculo-venous shunt was done 41 times in 27 patients, of whom 7 have died. This rate of success of 70% is about the same as in the hands of others, and compares with the 40%–50% rate of "arrest" that others have observed in non-operated hydrocephalics. This 20% to 30% decrease in mortality is sufficient to allow the conclusion that ventriculo-venous shunts are of value in the treatment of infantile hydrocephalus. When the procedure is carried out at an early age, decreased morbidity also may follow.

Surgery of Endometrioma of the Ileum and Colon. C. Davis, Jr., O. Akre and R. E. Buenger. *American Journal of Surgery 105, No. 3, March, 1963.*

The subject of endometrioma of the small and large intestine associated with intestinal obstruction is discussed. The clinical manifestations, the treatment, and the associated pathology are presented pertinent to ten patients with involvement of the intestine by an isolated endometrioma.

A number of important features concerning endometrioma of the small or large intestine are stressed. The occurrence of obstructive symptoms, accentuated preceding or during the menstrual period, should suggest an endometrioma in the differential diagnosis of intestinal obstruction. An endometrioma of the small or large bowel can be diagnosed on an awareness of the possibility of the disease, a complete history and a combined rectovaginal examination coupled with the findings of the proctoscopic and barium examinations. The gross appearance as well as the symptomatology of an endometrioma and a carcinoma of the colon are similar so that it is often difficult to distinguish these lesions even at operation.

It is recommended that the management of patients with a solitary endometrioma or multiple endometrial implants affecting the intestine should be individualized. The choice of treatment depends upon the age of the patient, the evaluation of the severity of the symptoms and the extent of the involvement of the small and large intestine as well as the pelvic organs. The preservation of ovarian function is advocated whenever possible.

The Occurrence of Carcinoma in "Hot" Thyroid Nodules. Report of Two Cases. F. O. Becker, P. G. Economou, and T. B. Schwartz. *Annals of Internal Medicine, May, 1963.*

It is generally accepted that thyroid nodules showing hyperfunction on the scintogram are not malignant. Exceptions to this general rule do occur and two patients with solitary hyperfunctioning thyroid nodules which histologically revealed papillary carcinoma within an adenoma are presented. Radioautographs show no uptake over the tumor cells but increased uptake in the surrounding parenchyma. The first patient had a hard thyroid nodule and symptoms suggestive of hyperthyroidism but without other physical or laboratory findings to support this diagnosis. The clinical impression was malignancy. The second patient was asymptomatic except for a thyroid nodule which did not suppress with L-triiodothyronine, suggesting that the nodule was autonomous. Surgery was performed in each instance as a result of total clinical evaluation rather than reliance on the results of the scintogram alone. Although it seems likely that the presence of malignancies within hyperfunctioning nodules is rare, the finding of a "hot" nodule does not, of itself, preclude a diagnosis of carcinoma.

Osteogenic Sarcoma in a Luminous Watch Dial Painter. C. Davis, Jr., R. Brown, and R. W. Alexander. *Archives of Surgery 86, pp. 190–195, February, 1963.*

The history and findings are presented of a 52-year-old female who developed a radiation osteitis of multiple bones and an osteogenic sarcoma of the right ilium which proved fatal. The patient had been treated over a period of years for "rheumatoid arthritis" involving the shoulder and hip joints. Considerable pain and limitation of motion were experienced in spite of medical therapy.

After the possibility of a thyroid carcinoma with metastases to bone was eliminated as a cause of the marked bone changes, and after the history of radium contact was established, further surgery revealed an osteogenic sarcoma of the right ilium. Roentgenograms of the long bones, vertebral bodies, and pelvic bones with destruction of both acetabula demonstrated the characteristic pathological changes resulting from irradiation of bone.

Of interest is the fact that the patient was unaware that she had received a harmful dose of radioactivity as a result of her occupation as a watch dial painter 30 years earlier.

Bifurcational Anastomosis of Small Arteries with Pedicled Grafts. G. de Takats. *Surgery, Vol. 53, No. 3, pp. 340–343, March, 1963.*

A pedicled graft was used to restore patency not only to the main channel, but to an important branch. The point of anastomosis was at the origin of the saphenous artery from the femoral.

With the use of a magnifying lens, fixation and stay sutures, and no anticoagulants, one half of the saphenous arteries with an average external diameter of 1.4 mm. remained open. This type of graft may be applicable at the level of the profunda femoris and at the origin of the sural and peroneal branches. An autogenous vein seems the most suitable material for the reconstruction of small arteries.

Selective Inactivation of Fibrin Stabilizing Factor Contaminant in Fibrinogen. S. Swigert, J. L. Koppel and J. H. Olwin. *Nature, 198, 797, 1963.*

Fibrin stabilizing factor (FSF, fibrinase) is a thermolabile plasma protein which in the presence of calcium converts a loosely cross-linked, urea soluble fibrin clot (fibrin s) into a urea-insoluble gel (fibrin i). Although simple clot solubility tests allow the detection of qualitative differences in the structure of fibrin or plasma clots the quantitative determination of fibrinase activity is complicated by the difficulty of obtaining fibrinogen preparations not containing this enzyme in active form. It has been observed that fibrin stabilizing factor, present in purified bovine and human fibrinogen preparations, can be selectively inactivated by treatment with mercaptide-forming agents such as p-chloromercuribenzoic acid or Salyrgan without apparently altering the reactivity of the fibrinogen itself. A method has been developed in which both FSF inactivation and fibrinogen labelling with fluorescein are carried out simultaneously thereby producing a labeled fibrinogen product suitable for use in an assay system for the quantitative measurement of FSF activity.

Bone Grafts: Cellular Survival Versus Induction. R. D. Ray and T. Y. Sabet: *The Journal Of Bone And Joint Surgery. Vol. 45-A, No. 2, pp. 337, 344, 1963.*

By using tritiated thymidine as a cellular label, it has been shown that when the femora of inbred newborn mice are transplanted as isografts, both the cells of the graft and of the host contribute to the new-bone formation that occurs in the ensuing two weeks. In the case of the homografts, the new-bone formation in this time interval is limited and is derived primarily from the cells of the graft rather than from the host.

Observations on the in vitro Effects of Chylomicra, Low-Density Lipoproteins and Phospholipids on Human Plasma Euglobulin Lysis. A. R. Pappenhagen, J. L. Koppel and J. H. Olwin. *Thromb. Diath. Haem., 9, 164, 1963.*

Data have been presented on the in vitro effects of human chylomicra, low-density human plasma lipoproteins, and partially purified preparations of various phospholipids on human plasma euglobulin lysis. Euglobulin lysis was found to be accelerated by preparations of mixed soybean phospholipids (asolectin), cephalin, phosphatidyl inositol, phophatidyl serine and phosphatidyl ethanolamine. In contrast, it was found to be inhibited by preparations of human chylomicra, low-density human plasma liproproteins and lecithin. Inhibition of euglobulin lysis produced by any of these three agents could be diminished or completely overcome by the simultaneous presence of suitable levels of any one of the accelerating agents. In all cases studied, both inhibitory and accelerating effects were observed to be concentration-dependent. Evidence has been obtained to suggest that in the case of the accelerating agents the observed increased rate of euglobulin lysis is not a direct effect on lysis itself, but rather is due to more complete precipitation of plasminogen in the presence of these substances. On the other hand, it appears that the inhibitory effects observed are not related to the extent of plasminogen precipitation, but are actually true inhibitions of euglobulin lysis. The possible clinical significance of some of these observations has been briefly discussed.

Sparteine Sulfate and Rupture of the Uterus. Report of a Case. H. Boysen. *Obstetrics and Gynecology, Vol, 21. No. 4 April, 1963.*

1. A case of rupture of the uterus following the use of sparteine sulfate for the stimulation of labor is reported.
2. Sparteine is an oxytocic drug that is not "harmless."
3. The same dangers inherent in the use of any oxytocic drug in labor pertain to the use of sparteine sulfate.
4. The same precautions and regulations that govern the use of any oxytocic agent should be applied to the use of sparteine sulfate.

Solubilization of Fibrin s by Phospholipids. A. R. Pappenhagen, J. H. Olwin and J. L. Koppel. *Proc. Soc. For Exptl. Biol. & Med., 112, No. 3, 741, March 1963.*

The mechanism by which phosphatidyl inositol, phosphatidyl serine or other substances dissolve fibrin s is unknown. Of the phosphatides tested, only those with acidic characteristics are effective. It may be primarily this property which promotes rupture of the secondary hydrogen bonds holding the fibrin strands in the loose network of the fibrin s clot. When calcium is present, fibrin-stabilizing factor (present in most fibrinogen preparations) gives rise to fibrin i by cross-linking these fibrin strands and thereby making them resistant to the action of solubilizing agents.

The extent of solubilization progressively diminishes with increasing ionic concentration of the system, but is not significantly influenced by the type of buffer.

Therefore, in order to avoid possible misinterpretation of fibrinolytic activity data obtained with the fibrin plate method it would appear essential that a) only fibrin i preparations be used in such tests, and b) the ionic concentration of the fibrinogen solution used be carefully standardized and controlled.

Antitumor Action of Several New Piperazine Derivatives Compared to Certain Standard Anticancer Agents. T. J. McNair, F. A. Wibin, E. T. Hoppe, J. L. Schmidt and F. A. dePeyster. *J. Surgical Research 3, 130, May 1963.*

This report details the results of a study designed to compare the antitumor action of three new piperazine compounds to nitrogen mustard (HN_2) and 5-fluoro uracil (5-FU) against established and disseminated tumor cells in rats and mice.

Of the three piperazine derivatives tested, bromopropionyl piperazine (A 8103) appeared to be most effective and superior to HN_2 or 5-FU against Walker 256 tumor in the rat.

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ERYTHRASMA
Its Possible Relation to Red Fluorescence in Squamous Cell Carcinoma

Nicholas L. Tilney, M.D.
Roger L. Mehl, M.D.

Small areas of the ulcerated surfaces of squamous cell carcinomas have been reported to fluoresce bright red when placed under the Wood lamp. Erythrasma, a moderately large rod-shaped bacteria, has likewise demonstrated red fluorescence under this light in contrast to that emitted by other organisms. Since these two entities have not been reported as occurring together, the following case is presented.

It is suggested that Erythrasma may be more common than heretofore supposed, and that this organism may contribute to the fluorescence of ulcerated lesions.

A 41 year old Negro male entered the hospital for the diagnosis and treatment of a lesion on his scalp. Since birth there had been a small, asymptomatic, raised area on his head, varying in color from red to white. Three years before admission he had struck this lesion while at work, cutting off its top. Subsequently he had noted rapid growth of the still asymptomatic lesion, with associated partial alopecia within and around the area. The patient had lived in Chicago most of his life and had never travelled south of Kentucky. He had not left the United States.

Physical examination was unremarkable except for a circular scalp lesion 8 cms. in diameter. This had a high, rolled, erythematous, serpiginous border up to 1 cm. thick. The center showed crusting and scaling (Fig. 1). The lesion was non-tender, and no cervical adenopathy was demonstrated. Admission laboratory studies of blood and urine were normal. Four separate biopsies were taken of the area. Repeated microscopic examination showed only hyperkeratosis and chronic inflammation. Cultures consistently grew light growths of coagulase negative Staphylococci and beta hemolytic Streptococci. Cultures for fungi and tuberculosis were negative. The patient's Wasserman test and skin tests for Blastomycosis, Coccidiomycosis, Tuberculosis and Histoplasmosis were all negative. A chest roentgenogram was normal. Under Wood light portions of the lesion fluoresced bright red.

The lesion was finally excised in its entirety, including some free skin margin. A split thickness graft was employed to cover the defect and the patient went home after an uneventful post-operative course. Only the surface of the excised tissue was found to fluoresce red in cross-section under the Wood lamp. The pathological diagnosis was squamous cell carcinoma, and later a profuse growth of Erythrasma was cultured from a media of liver and hormone.

From the Division of Surgery.
Cultures prepared by H. MacLean, Research Assistant in Microbiology.

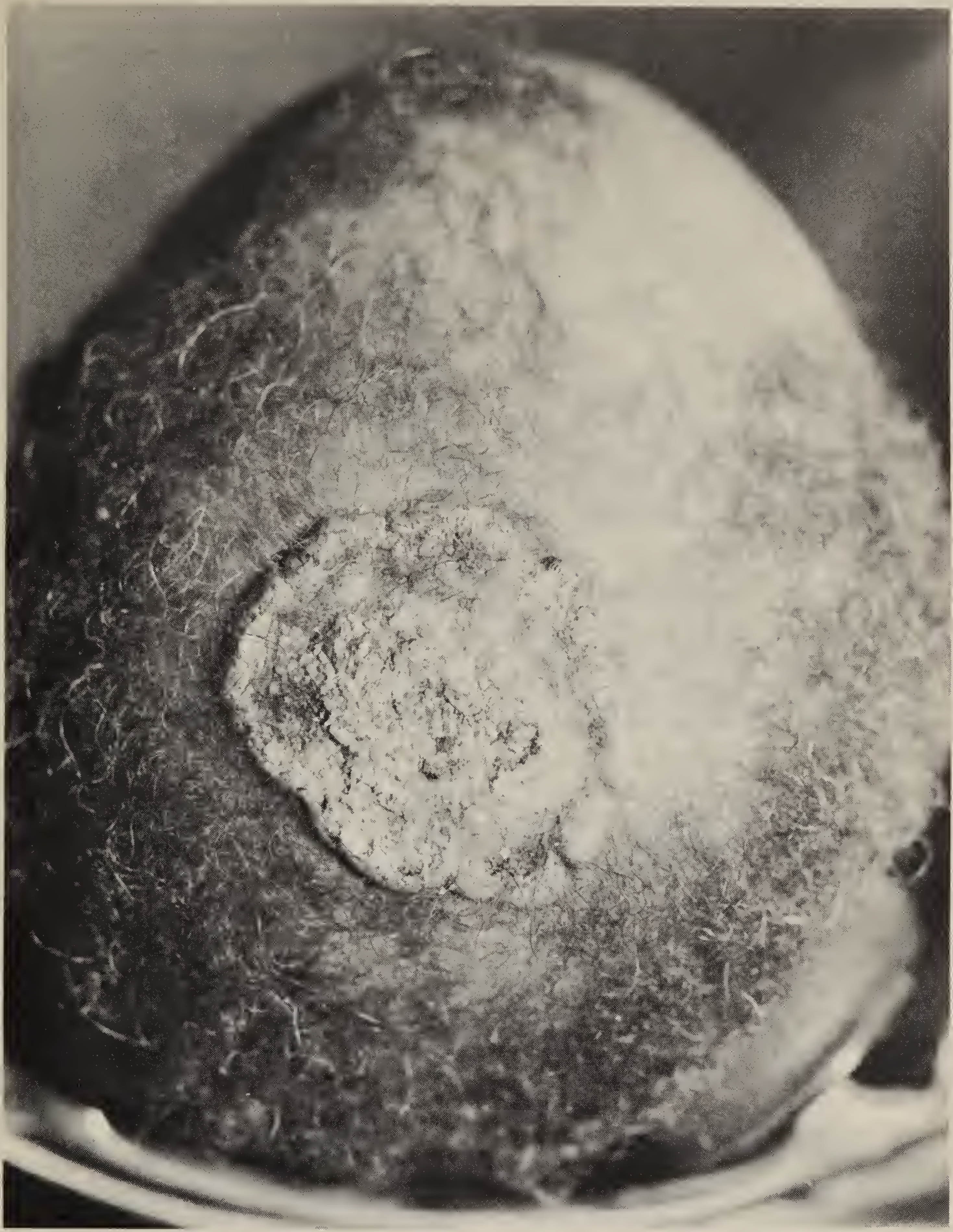

Fig. 1—View of top of head demonstrating scalp lesion

DISCUSSION

The necrotic surfaces of squamous cell carcinomas, ulcerated adenocarcinomas of the breast, fibrosarcomata and chondrosarcomata have been shown to emit bright red light under the Wood lamp.[1] This contrasts to that fluorescence shown by other superficial lesions of skin; basal cell epithelioma, inflammatory lesions and granulomata which rather uniformly fluoresce dark purple under the light. The entity thought responsible for the fluorescence of experimentally produced squamous carcinoma as well as the tumors mentioned is a protoporphyrin or coproporphyrin[2,3], which emits light of similar wave length as that of tumor debris.

Because of difficulties with the culture and growth of the organism, Erythrasma has only recently been shown to be a bacterium, possibly a Corynebacterium.[4] It is commonly found in the skin creases of the toes, genitocrural and other intertriginous areas of the body, although it has not been reported as occurring on the head. It thrives in tropical and warm climates and is treated successfully with systemic Erythromycin. The cherry red fluorescence under Wood light is considered pathognomonic for Erythrasma. This phenomenon is as yet unexplained except that the porphyrins, notably uroporphyrin, have been implicated.[5]

The observation that only the ulcerated surface of squamous carcinoma fluoresces and not the cut cross-section, raises the question whether a secondary invader, Erythrasma, causes the atypical fluorescence of these tumors rather than only components of the tissues themselves as was previously thought. The above case is presented to suggest Erythrasma as a scource of the red fluorescence in these tumors.

SUMMARY

A case of squamous cell carcinoma of scalp is shown in which Erythrasma was identified as a secondary invader. Their common red fluorescence is discussed.

ACKNOWLEDGEMENT

The authors wish to thank Dr. John B. Haeberlin of the Department of Dermatology for his assistance in the preparation of the manuscript.

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SUBACUTE BACTERIAL ENDOCARDITIS

Preliminary Observations On The Efficacy of A Newly Utilized Parameter In Its Differential Diagnosis

Robert Devetski, M.D.
Charles Vygantas, M.D.
Mark H. Lepper, M.D.

During the latter part of 1962, we became particularly interested in the apparently increased numbers of patients who were presenting with a problem of known cardiovascular disease in the past, and who now were manifesting questionable evidence of an endocarditic process. In a significant number of these individuals, after an extensive work-up had failed to elucidate more specifically their clinical problem, antimicrobial therapy of the "short-course" and, in some instances, even "long-term-treatment" type was initiated. The outcome, not unexpectedly, was all too frequently an unsuccessful one.

Since in a significant number of these cases there was no leukocytosis, no increase in immature granulocytes, no measurable disturbance of hepatic function, and the individuals were for the most part under the age of forty-five, we directed our attention to seeking out a new parameter which might assist us in distinguishing between infectious and non-infectious febrile episodes in culturally negative and previously well-documented cases with cardiovascular lesions. Such a test would not necessarily be considered the *sine qua non* of the disease process, nor would it assume the magnitude of a positive blood culture. But in the presence of one or more cardiac murmurs, a daily febrile reaction, questionable lienomegaly, and perhaps an elevated erythrocyte sedimentation rate—such a test might well provide a valuable adjunctive diagnostic aid to the physician in his ultimate decision concerning the efficacy of treatment in any given situation.

The impetus for this study thus becomes obvious, and its direction was provided by the knowledge of a frequently associated phenomenon, namely, increased amounts of the enzyme, alkaline phosphatase, in the cytoplasm of cells from the granulocyte series, in the peripheral blood smears of patients with acute inflammatory disease.[1-3] The most significant work relative to this observation was that of the Australian physician R. G. Wyllie[4]. He was able to demonstrate a rather significant degree of correlation between the level of LAP (leukocyte alkaline phosphatase) and the presence, activity, and extent of acute inflammatory processes. He pointed out the influence of steroids and antibiosis, as well as the chronologic variability in levels of LAP.

From the Division of Medicine and from the Department of Preventive Medicine, University of Illinois College of Medicine.
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In this study, we have attempted to provide a preliminary evaluation of the applicability of such a histochemical test as a means of more accurately classifying the various etiologic factors involved in fevers occurring as "Endocarditic Equivalents".

MATERIALS AND METHODS

The patient population for this study consists of approximately equal numbers from the Presbyterian-St. Luke's Hospital, the University of Illinois Research and Educational Hospitals, and the Municipal Contagious Disease Hospital, all of Chicago, Illinois. The total number of patients was divided into three groups: 1. afebrile, control, or normal, 2. acute, febrile illnesses of culturally proven bacterial origin, 3. febrile patients with known cardiovascular disease. They represented all points of the spectrum of endocarditis insofar as clinically suspected, or culturally confirmed cases are concerned.

Peripheral blood smears were obtained through the cooperation of the various clinical laboratories, and a clinical history was obtained for each individual. The slides were then stained utilizing the cobalt-ammonium sulphide technique of Gomori-Takamatsu[5,6] with Kaplow's modification.[7] The "Kaplow Count" is a semiquantitative determination, and is based on the original criteria as established by Kaplow. One-hundred granulocytes are counted under the high dry lens (440 X) of a binocular scope. Each cell is graded from "0" to "4+" on the basis of the degree and extent of dark brown pigment which is visible in its *cytoplasm.* At the end of each scan, the number of cells is multiplied by the graded number and totaled, to arrive at a "Kaplow Count". A normal count by our established technique was from 0–60. After the final step in the staining had been accomplished, one individual, other than the two persons who ultimately read the slides and determined the "Kaplow Count," randomly labeled and tagged the slides with code numbers. Both the clinical records and the code remained in the "third" person's hands until each microscopist had read first his half of the slides, and secondly his partner's half. At that time the codes, clinical material, and readings were turned over to a fourth individual who tabulated and evaluated the data.

RESULTS

As outlined in Table 1, it becomes readily apparent that by any of the commonly accepted tests of statistical significance, the LAP levels certainly parallel the findings as previously described, and remain quite consistent with the presence or absence of an acute inflammatory process.

The microscopic appearance of the granulocytes as might be observed in a "scanning view" of a peripheral blood smear is demonstrated in Figure 1. The artefactual appearance of the red cells is attributable to the staining process, but

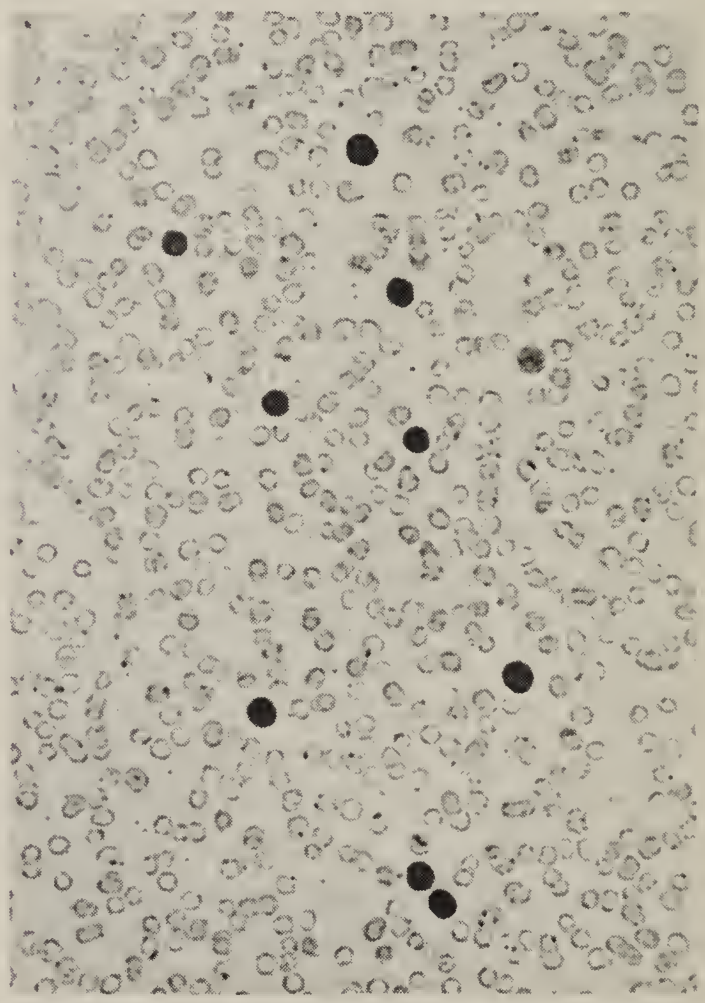

Fig. 1—The microscopic appearance of the granulocytes as they appear in a "scanning view" of a peripheral blood smear prepared for a "Kaplow Count."

TABLE 1

Group	Total Pts./Pts. of Record	Kaplow Units** Arithmetic Mean	Range of LAP (leukocyte alk. phos.)	Ages (range, years)	Sex ratio	Total WBC (range)	Temperature at time slide was taken	On Steroids (or) Surgery within Previous 10 days
I Afebrile, Controls, (or) Normals	9/8*	30	19-58	26-61	1.8 : 0.7 ♀	4–7($\times 10^3$)	98.6°F	None
II Acute, Febrile with Culturally Proven Bacterial Origin	19/19	140	80-330	1-76	1.5 : 1.3 ♂	6.6–27($\times 10^3$)	98.6°F–105°F	None
III Febrile with Known Cardio-Vascular Disease	18/17*	110	45-230	18-61	1.4 : 1.1 ♂	5.1–16($\times 10^3$)	99°F–101°F	None

*Discrepancy Explained in Text **Kaplow Units (see Text)

creates no interference with visualization of the deeply pigmented cytoplasm of the white blood cells. An intermediate cell can be visualized in the upper left quadrant of the field and would be interpreted as a "2+" for purposes of determining quantitatively the "Kaplow Count."

Figure 2 gives a more representative view of the cells as visualized by the microscopists and demonstrates as well the previously noted facts that the granulocytic series stains rather deeply and for the most part, when a slide is "positive," the majority of the cells will be noted to fall into the 3+ or 4+ category. Likewise it has been uncommon for us to see more than an occasional cell with greater than a 2+ degree of staining if the slide was negative.

One of the "control patients" was noted to have an elevated LAP (124 units). We investigated this patient's clinical history further and in view of his age, the diminished level of hemoglobin recorded, and his diagnosis of "colitis," could only suggest to his physician the possible merit of a more extensive gastrointestinal examination. Another patient listed in the "possible SBE" category was an adult young woman, who, following more extensive investigation, was concluded to have multiple (non-septic) pulmonary emboli. Her "Kaplow Count," on two occasions, was within normal limits.

Another patient within the group of suspect SBE patients, was a middle-aged man who had had known rheumatic heart disease for a number of years, and had received several courses of antibiotic therapy while hospitalized on as many occasions within the past six months. Serially one could observe the marked fluctuations in his count as antibiotic therapy would suppress but apparently never completely eliminate the nidus of infection which persisted in spite of our efforts. Whenever antibiosis was interrupted, the count rose sharply only to fall again (within 24-48 hours) with re-initiation of treatment. This last point is one which should be re-emphasized since it could definitely influence the levels one would observe in patients with SBE were they to be treated with suppressive drugs before the peripheral smears were obtained. More emphasis on this point will be provided in the next section of the paper.

One other significant point from the results that is not obvious from scanning

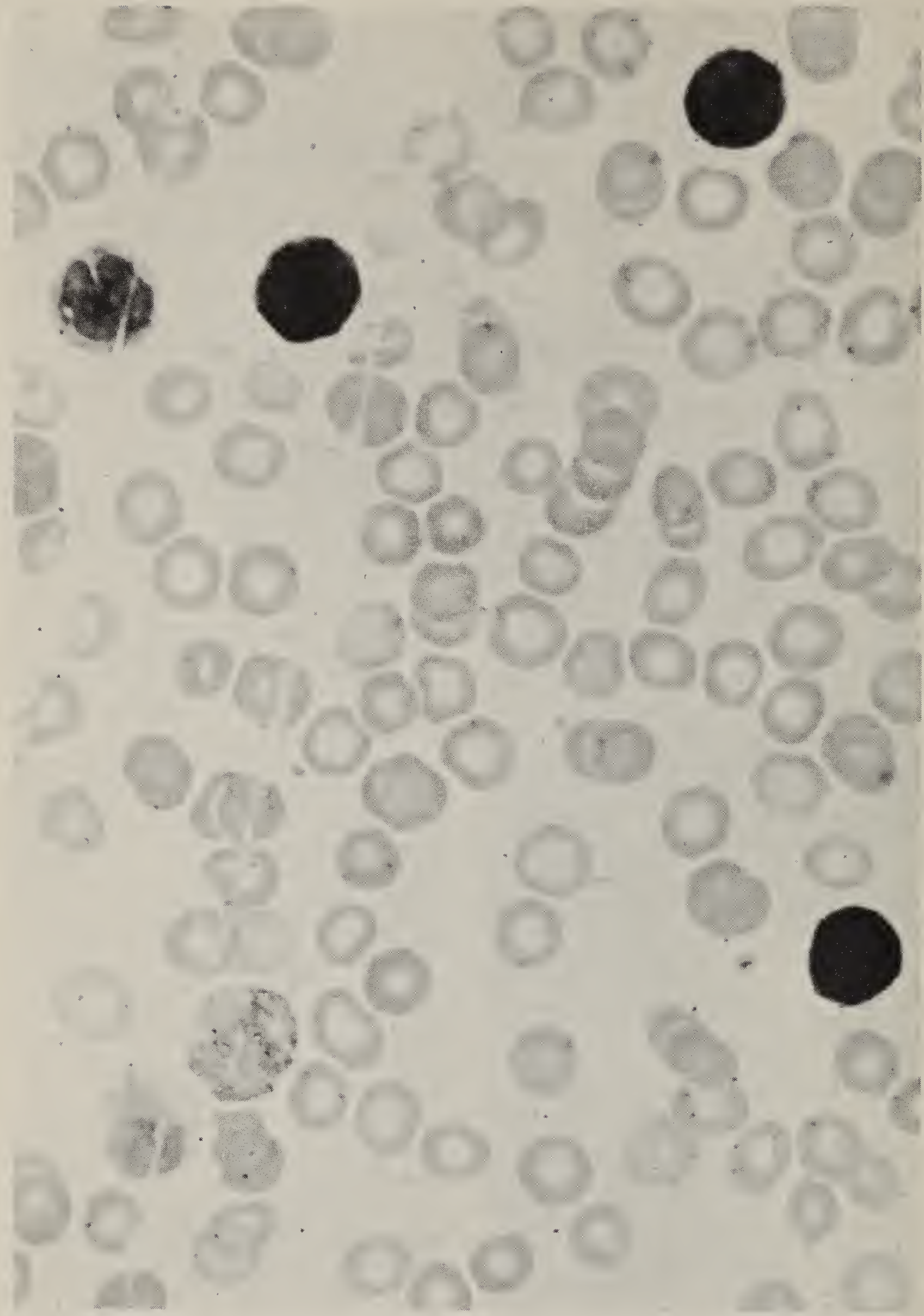

Fig. 2—This view demonstrates the deep staining of the granulocytes.

Table 1 is that the levels of LAP were completely unrelated to the level of the WBC. Some of the highest "Kaplow Counts" were observed in patients with white blood counts between 5,000 and 10,000/cmm. In several of the total of 46 patients, the serum alkaline phosphatase was checked and found to be likewise unrelated to the levels as registered by the "Kaplow Count".

DISCUSSION

The influence of progressively more elaborate cardiovascular manipulations by both internist and surgeon on the incidence of subacute bacterial endocarditis, or what we have referred to as "endocarditic equivalents," cannot be stated at this time.[8] From our own observations in the laboratory, it would seem that, insofar as the "very probable" cases of endocarditis is concerned, we are seeing a greater number associated with organisms of rather low degrees of pathogenicity.

The problem of evaluating a patient for the possibility of a diagnosis of SBE has always been a difficult one. The urgency for establishing more definite and objective criteria *before* chemotherapy is introduced cannot be over-emphasized. We consider from our preliminary observations as outlined in this paper that the use of this semi-quantitiative histochemical test for a leukocyte enzyme —alkaline phosphatase—provides a valuable diagnostic adjunct which should be made available to the physician. For, in spite of the tremendous advances which have been made in the past two decades in the area of antibiotic therapy, we cannot hope to achieve a successful outcome with treatment in 60% to 75% of cases[9] until better definition, and diagnostic criteria, as well as a more rational and intelligent use of the agents at hand, are established.

SUMMARY

In an attempt to distinguish between fevers of infectious and non-infectious origin, which develop in patients with know cardiovascular disease, and from whom no positive blood cultures can be obtained, we have utilized the stain for leukocyte alkaline phosphatase.

With semi-quantitation we observed a statistically significant degree of correlation between the presence of active inflammatory disease—whether it be in "acute bacterial infections" or smouldering cases of "subacute bacterial endocarditis"—and the height of the LAP level.

ACKNOWLEDGEMENT

The authors express their thanks to Norman Ream, M.D. for his assistance in obtaining some of the clinical data included herein.

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EXPERIMENTAL PANCREATIC FISTULA

Comparative Secretion of Antibacterial Agents in the Dog

EDWARD A. DAINKO, M.D.*
ANDRES GABEL, M.D.
HAROLD A. PAUL, M.D.
EDWARD J. BEATTIE, JR., M.D.

The ideal pancreatic fistula would be one through which the entire flow of pancreatic juice could be directed in its pure form with no alteration in the pancreas itself. While there have been no instances reported of the study of antibacterial agent secretion by the canine pancreas, there have been studies reported of antibacterial agent secretion in pancreatic juice from accidentally occurring human pancreatic fistulas.[1-9] This study is concerned with the development of an improved method of collecting total pancreatic secretion and to evaluate the pancreatic secretion of certain antibacterial agents.

METHODS

Surgical Technique: Female mongrel dogs weighing 11 to 16 Kg were selected. All dogs were anesthetized with intravenous pentobarbital sodium. The pancreatic fistula was constructed in two stages; (1) hemisection of the urinary bladder,[10] and (2) duodenopancreaticopyelostomy.

The urinary bladder and urethra were exposed through a suprapubic midline incision. The urethra was divided between two silk ligatures (Fig. 1a). The anterior wall of the bladder was opened and the two ureteral orifices visualized (Fig. 1b). The bladder was bisected, taking care to include one ureteral orifice in each half of the bladder (Fig. 1c). Each hemibladder was sutured through and through with 4-0 chromic catgut and a urinary catheter inserted into each (Fig. 1d). This suture line was oversewn with a continuous seromuscular stitch of 3-0 black silk. A stab wound was made on each side of the incision lateral to the rectus abdominis muscle and the catheters brought through the abdominal wall. Each bladder was sutured to the peritoneum around the catheter (Fig. 1e). The abdominal wall was closed in layers with 00 chromic catgut.

One week after the hemisection of the urinary bladder a subcostal incision was made in the right upper quadrant. The duodenum and pancreas were exposed and the main pancreatic duct located.[11] The pancreas was dissected free from the duodenum, (Fig. 1f), while avoiding injury to the pancreas with its intact blood supply. The common bile duct was identified and avoided. The lesser pancreatic duct and any additional pancreatic ducts were ligated and divided. A two-centimeter round cuff of duodenal wall containing the papilla of the main pancreatic duct was excised from the duodenum

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From the Division of Surgery.
*At present Robertson Traveling Fellow, London Hospital, London, England.

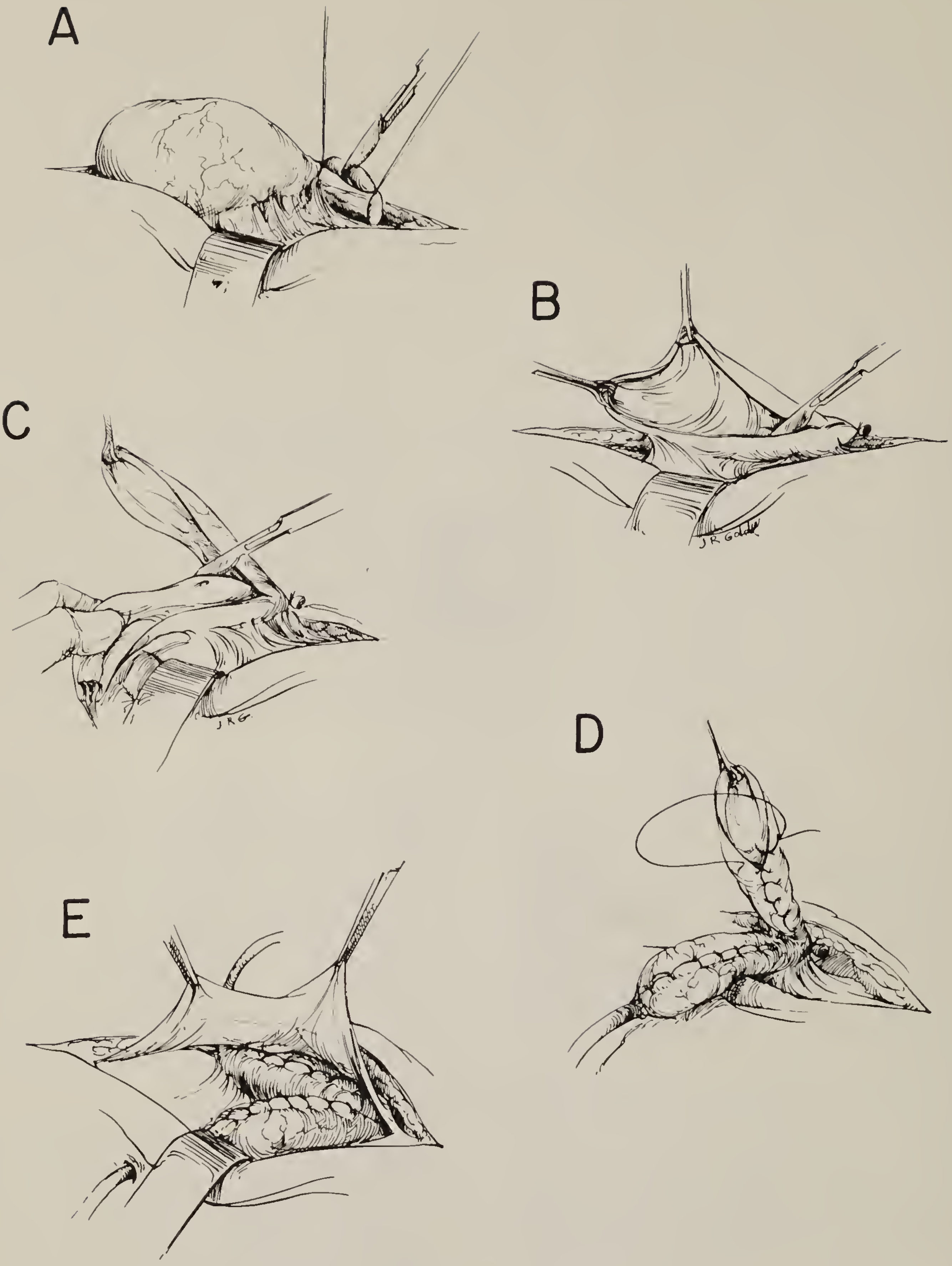

Figure 1.—FIRST OPERATION

a Urethra is divided between ligatures.

b. Bladder incised, anterior wall.

c. Posterior wall is divided between ureteral orifices.

d. Closure of two hemibladders over catheters.

e. Peritoneal closure; counterincision for catheter.

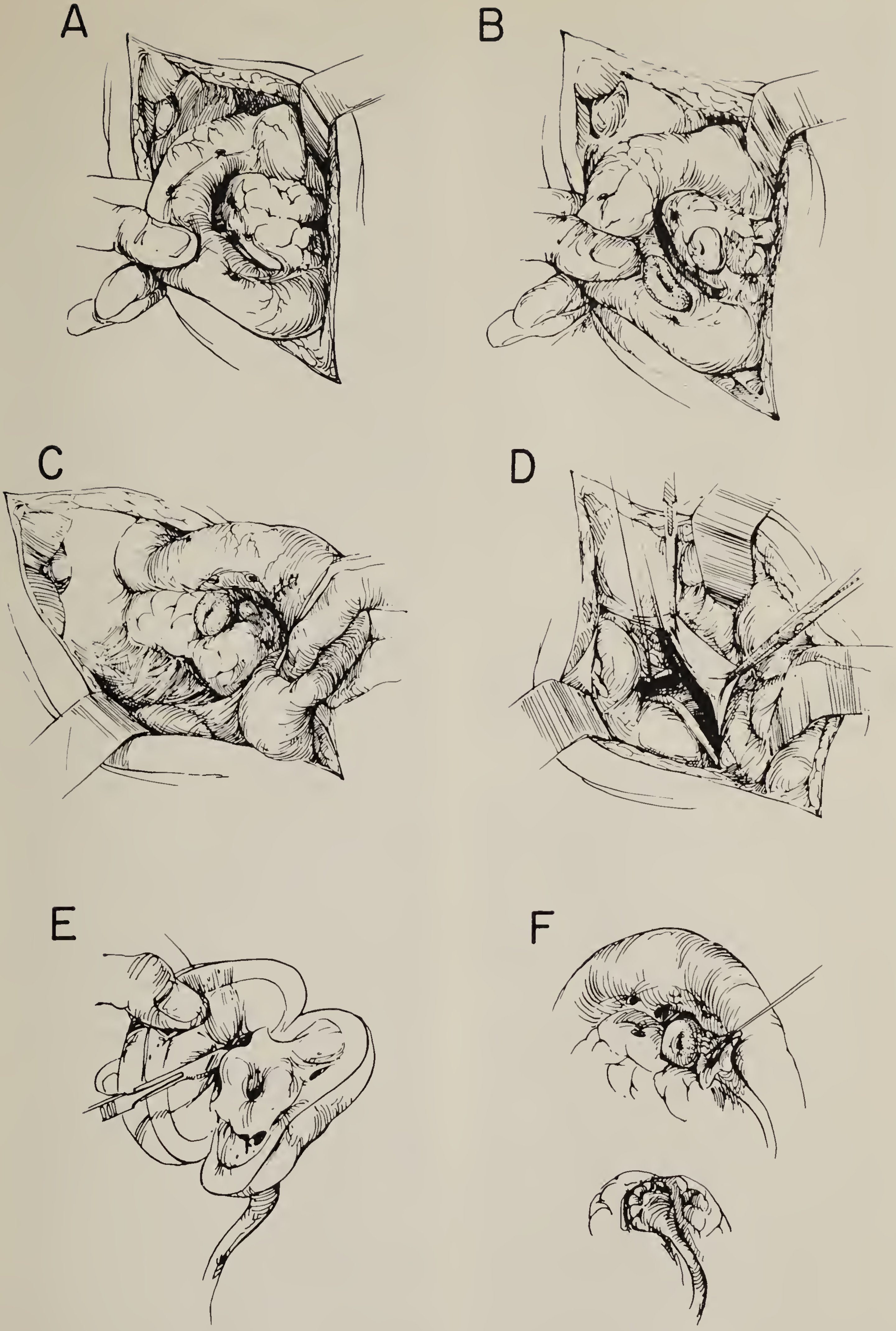

Figure 2.—SECOND OPERATION
- a. Main pancreatic duct isolated.
- b. Duodenal "button" removed.
- c. Duodenotomy closure.
- d. Right renal vascular supply is divided.
- e. Preparation of renal pelvis.
- f. Pancreatico-ureteral anastomosis.

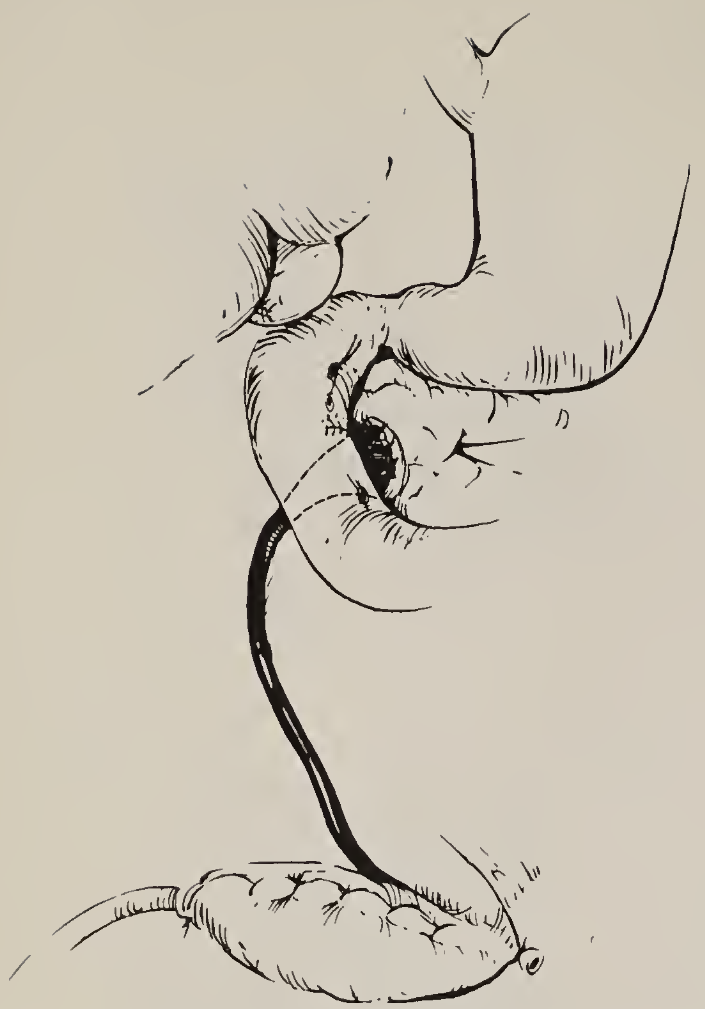

Fig. 3.—The illustration shows the completed duodenopancreatico-pyelostomy for the total flow of pancreatic juice into the right urinary collecting system.

(Fig. 2a). The duodenum was closed transversely with continuous 3-0 chromic catgut and interrupted 4-0 black silk. The duodenal cuff was then stripped of its mucosa and placed posterior to the duodenum (Fig. 2b). Hemostasis was attained on the surface of the cuff by pressure.

The parietal peritoneum over the right renal pedicle was then incised. The renal artery and vein were ligated and divided between silk ligatures (Fig. 2d). The kidney was mobilized into the wound. The peripheral one half of the kidney was excised, and the excess renal tissue was removed from the renal pelvis (Fig. 2e). The renal pelvis was anastomosed to the duodenal cuff with continuous 4-0 chromic catgut. An outer layer of interrupted 5-0 black silk sutures reinforced the inner catgut layer (Figure 2f).

The duodenum, pancreas, ureter and the anastomosis were replaced in a normal position in the right upper quadrant and the omentum placed over them (Fig. 3). The abdomen was then closed in layers.

Collections were made by means of plastic bags attached firmly to the catheters within linen jackets. The bags could be emptied at will through a second tube at the opposite end of the bag.

Study of Antibacterial Agents: The antibacterial agents selected for study in the pancreatic secretion after intravenous injection were colistimethate sodium, kanamycin sulfate, erythromycin glucoheptonate, sulfisoxazole diethanolamine and nitrofurantoin sodium.

Colistimethate sodium, 25 milligrams, was administered to three animals. Blood samples were obtained aseptically by venipuncture before and after the infusion. Pancreatic juice samples were also collected before and after the infusion from the catheters in the right hemibladders. The specimens were collected at intervals of ½, 1, 1½, 2, 5, 8 and 12 hours after the completion of the infusion. The blood was allowed to clot and the serum drawn off.

Kanamycin sulfate, 180 milligrams, was administered to two animals. Blood and pancreatic samples were collected at the same intervals as for colistimethate sodium.

Erythromycin glucoheptonate, 250 milligrams, was administered to two animals. Samples were collected as above.

Sulfisoxazole diethanolamine, 1.0 gram, was given to two animals. The blood samples were oxalated and stored along with the pancreatic juice samples at 4°C.

Nitrofurantoin sodium, 50 milligrams, was given to two animals. Samples were collected as above. An additional injection of nitrofurantoin sodium was given to one of the dogs four days later with double the dose. Samples of urine were also collected from this dog.

Technique of Bioassay: Standard solutions of the antibacterial agents were prepared from commercially available vials. *In vitro* microbiological assay was performed using the tube dilution assay method. An Escherichia coli was used as the test organism for colistimethate sodium, kanamycin sulfate and nitrofurantoin sodium. A Staphylococcus-209P was used as the test organism for erythromycin glucoheptonate. Sulfisoxazole was assayed by the method described by Bratton and Marshall[12] for sulfanilamide.

RESULTS

Twelve female mongrel dogs weighing 11 to 16 kilograms were used in the experimental production of the internal pancreatic fistula.

The dogs on a regular kennel diet were noted to have watery, yellow, foul-smelling stools. These dogs rapidly lost weight and became cachectic. Their urine output and pancreatic juice output diminished until the time of death, 11 to 26 days after the production of the total pancreatic fistula. At the time of death all were found to have superficial ulcerations of the tongue, gastric antrum, duodenum and jejunum. Some areas of ulceration were more extensive than others. The distal esophagus and cardia of the stomach were found to be the site of ulcerations in one dog. Two dogs died of massive hemorrhage from the gastrointestinal ulcerations. Others were noted to have melena. At autopsy these emaciated dogs were obviously dehydrated. They were free of pancreatitis and no site of leak or obstruction was present along the fistula. Microscopic sections of the bladders and ureters were essentially the same bilaterally. At the point of duodenopancreatico-pyelostomy urinary epithelium was seen to line the duodenal cuff. The pancreas was not inflamed or atrophied. The pancreatic ducts were not dilated. Coliform bacteria and Staphylococci were present on multiple smears and cultures from both bladders.

A group of dogs maintained on bread, milk, pancreatic granules and intravenous electrolytes were found to deteriorate at a much slower rate. These dogs came to autopsy two to four months after completion of the fistula.

The results of the pancreatic secretion of colistimethate sodium, kanamycin sulfate, erythromycin glucoheptonate and sulfisoxazole diethanolamine are graphically shown in Figures 4 through 7. No active blood or pancreatic juice levels of nitrofurantoin was found in any of the dogs given 50 or 100 milligrams of the drug. The urine collected from the left kidney of the dog given 100 milligrams of nitrofurantoin sodium was found to contain 10 milligrams of the antibacterial agent in eight hours. The effect of pancreatic juice and serum on nitrofurantoin was tested. No decrease in the effectiveness of nitrofurantoin occurred in the sample incubated in serum, but the activity of the nitrofurantoin after incubation with pancreatic juice was diminished by about one-half. Alteration of pH was not attempted.

DISCUSSION

The two-staged preparation of a total internal pancreatic fistula is well tolerated by dogs. The dogs all suffer the effects of complete loss of the pancreatic secretion.

Urinary epithelium has been noted previously to epithelialize denuded gastrointestinal tract surfaces. [13,14] Urinary epithelium is relatively resistant to irritant material. The urinary epithelium covers the duodenal cuff stripped of its mucosa to prevent the admixture of the pancreatic juice with any *succus entericus.*

The fistula has the following advantages: 1) It is a total fistula. 2) It is composed entirely of epithelial-lined living tissue. 3) Strictures do not occur. 4) Autodigestion does not occur. 5) There is no pancreatic atrophy or duct dilatation. 6) The preparation can be made with minimal interference with the blood and nerve supply, unlike other experimental fistulas. [15,16] 7) The fistula can be kept free of infection, provided distal obstruction does not occur. During this study bacteria were consistently found in the hemibladders. It has been shown that the normal pancreas of dogs frequently harbor microorganisms. [17] 8) The fistula lends itself well to studies over extended periods of time. Manipulation of the du-

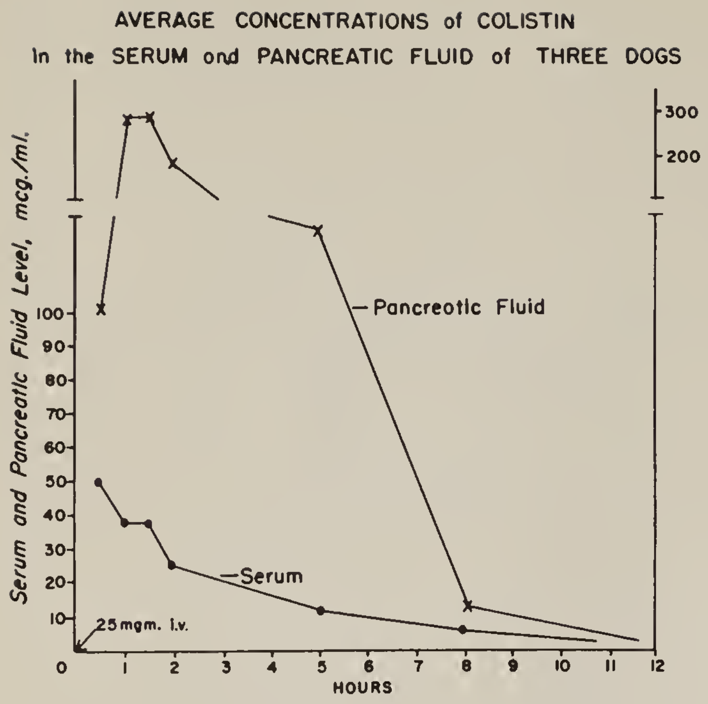

Fig. 4.—Twenty-five milligrams of colistimethate sodium was given intravenously to three dogs immediately after control determinations were obtained. The minimum inhibitory concentration of Colistin against the test organism was 0.3 micrograms per milliliter for all determinations. The average concentrations are shown.

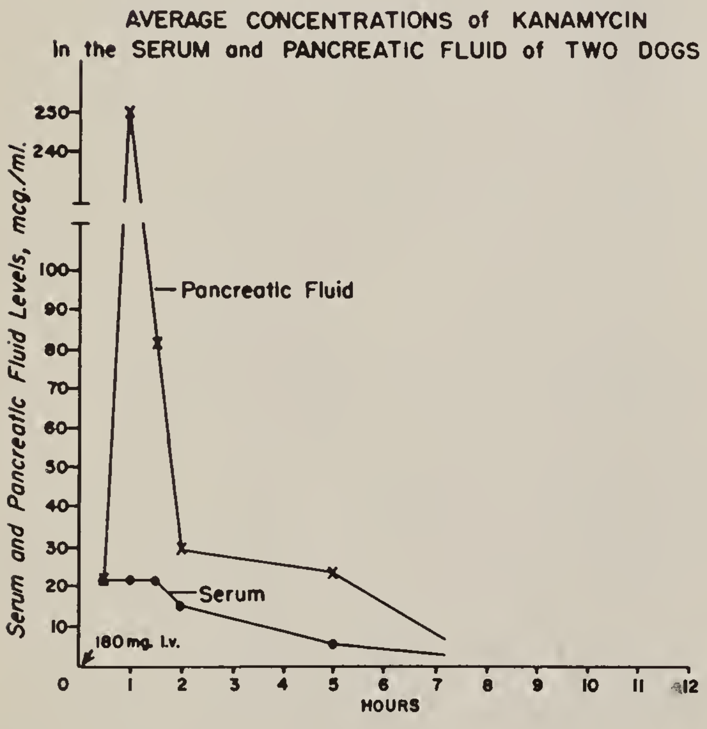

Fig. 5.—One hundred eighty milligrams of kanamycin sulfate was given intravenously to two dogs immediately after control determinations were obtained. The minimum inhibitory concentration of kanamycin against the Escherichia coli test organism was 2.6 micrograms per milliliter for all determinations. The average concentrations are shown.

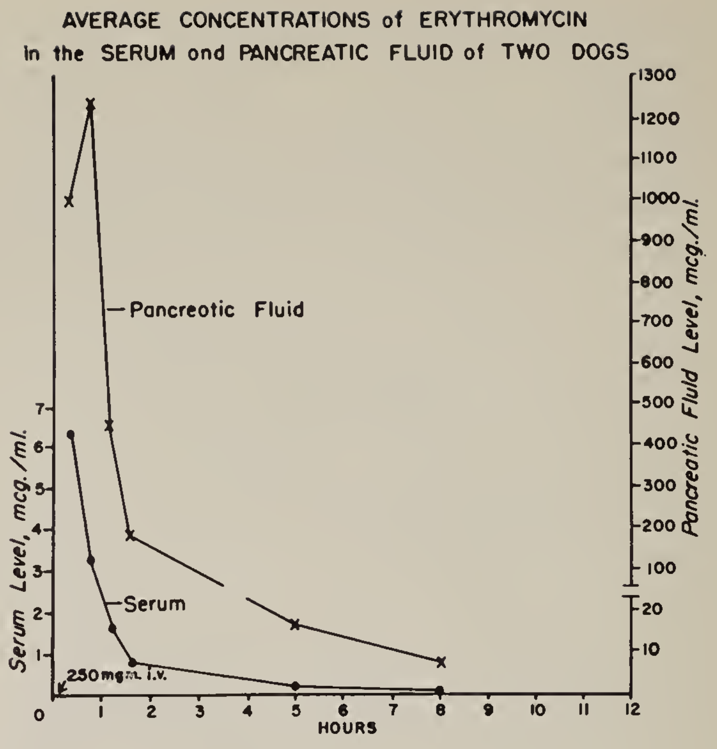

Fig. 6.—Two hundred and fifty milligrams of erythromycin glucoheptonate was given intravenously to two dogs immediately after control determinations were taken. The minimum inhibitory concentration of erythromycin against the Staphylococcus-209P test organism was 0.025 micrograms per milliliter for all determinations. The average concentrations are shown.

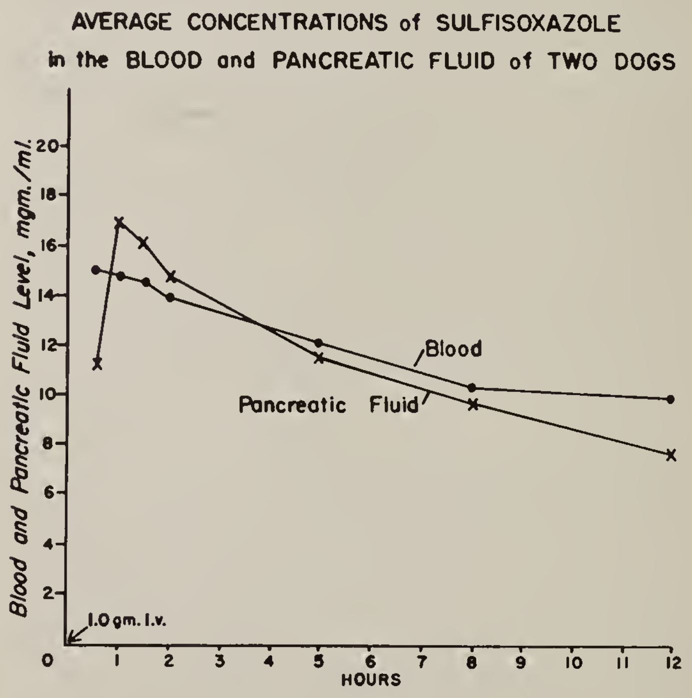

Fig. 7.—One gram of sulfisoxazole diethanolamine was given intravenously to two dogs immediately after the control determinations were obtained. The Bratton-Marshall[12] method for determination of sulfanilamide was used in obtaining the levels of each sample. The average concentrations are shown.

odenum or main pancreatic duct is unnecessary. All that is needed is a receptacle attached to the fistula catheter.

The occurrence of tongue ulcers in all twelve dogs was not thoroughly evaluated. They were noted to occur within the first 10 to 14 days after completion of the fistula. This observation does not seem to have been previously reported in association with total pancreatic fistula.

The administration of colistimethate sodium and kanamycin sulfate to fasting dogs resulted in higher levels of antibacterial activity in the pancreatic juice than in the blood at the same time. Since neither antibiotic is readily absorbed in the gastrointestinal tract[18–20] the pancreas is involved in excretion of these drugs and that an enteropancreatic cycle is not active in maintaining body levels of either. Schwartz[19] and his co-workers could demonstrate no significant difference in activity at pH 6, 7 or 8, although it has been reported[22] to be ten times more active at pH 6 than at pH 8. The aqueous kanamycin sulfate has a pH of 7.8 which is within the normal pH range of the pancreatic secretion[22,23].

In the two animals given intravenous erythromycin glucoheptonate very high levels of erythromycin activity were found in the pancreatic juice in the first two hours. With the dose given, effective levels were still present after eight hours. Erythromycin is readily absorbed in the alkaline environment of the intestinal tract[24] and the finding of a relatively high total output of erythromycin in the pancreatic juice points to an enteropancreatic cycle that must exist when the drug is given parenterally. The total amount of erythromycin excreted in the pancreatic juice of the two dogs was 6.4% and 6.1% of the total intravenous dose. This is more than tenfold higher than reported in humans.[1,6] In addition to the species difference, the incompleteness of the fistulas and concomitant disease of the pancreas associated with human pancreatic fistulas may be explanations for the higher secretion found in the dog.

Sulfisoxazole was found in the pancreatic juice in levels just slightly higher than in the serum. In man sulfonamides undergo variable degrees of acetylation which results in loss of activity. This does not happen in the dog[25] hence a higher and more prolonged sulfonamide level in the dog. Sulfisoxazole is absorbed in the intestinal tract,[24] thus an enteropancreatic cycle is active in maintaining the blood level.

The results found in the dogs given nitrofurantoin sodium support the findings of Halliday and Jawetz[26] in human subjects. Nitrofurantoin is carried in the blood largely in the bound, or otherwise inactive, form.[27] The antibacterial activity of nitrofurantoin is less at pH 7.5 than at pH 6 and this may, in part, account for the decreased activity of nitrofurantoin incubated in the pancreatic juice.

SUMMARY AND CONCLUSIONS

A new internal pancreatic fistula was produced for the collection of total pancreatic juice over an extended period of time.

Colistin, kanamycin, erythromycin and sulfisoxazole are actively secreted by the "resting" pancreas in free and active forms.

An enteropancreatic cycle is active in maintaining blood levels of erythromycin and sulfisoxazole.

The pancreas acts as a mode of excretion for colistin and kanamycin.

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HYPERCALCEMIA OF MALIGNANCY

Frank O. Becker, M.D.
Sydney Kofman, M.D.

INTRODUCTION

In viewing the problem of malignancy, one generally stresses its direct anatomic effects and tends to ignore complications secondary to metabolic effects, which may be of equal or even greater importance. One such example is hypercalcemia which is often fatal unless recognized and treated. Therefore, a review of the subject of hypercalcemia associated with malignancy appears in order.

OCCURRENCE

Hypercalcemia may occur in a variety of clinical states, including hyperparathyroidism, hypervitaminosis D, milk alkali syndrome, sarcoidosis, hyperthyroidism, immobilization, adrenal insufficiency, as well as in malignancy.[1,2]

A predilection of certain types of cancers, especially breast, lung and kidney for bone was demonstrated by von Recklinghausen[3] in 1891. The first report of an association between hypercalcemia and malignant disease was made in 1923 by Klemperer[4] in a patient with osteolytic metastases secondary to breast cancer. Several other early reports[5-8] noted this relationship but clinical interest was not aroused until Gutman[9] in 1936 observed hypercalcemia in a number of cases of multiple myeloma.

Woodford[10] described the incidence of hypercalcemia in a large series of patients with metastatic osseous cancer. It was 9.4% in 445 patients with breast cancer and was 8.9% in 135 patients with miscellaneous tumors (excluding multiple myeloma). Other series[11-13] revealed a similar frequency in spontaneous metastases. In patients with osseous metastases from breast cancer treated with sex hormones, the incidence of hypercalcemia is doubled, i.e. up to 20 per cent.[14,15] The occurrence of hypercalcemia is rare in both cancer of the thyroid and prostate metastatic to bone. In prostatic cancer, active osteoblastic activity may compensate for bone breakdown, while in thyroid cancer the slow growth of the tumor may account for the rarity of hypercalcemia.[12]

In the description of hypercalcemia of malignancy, separation of neoplasms into two separate categories is helpful in order to attempt to understand the various mechanisms operating in this clinical entity: 1) neoplasms with bony metastases, and 2) neoplasms without bony metastases. The first and by far the largest group includes not only the most common types of tumors that metastasize to bone, namely breast, lung and kidney, but also lymphomas,[16] leukemias,[17] and multiple myeloma.[9,10,18-20] Plimpton and Gellhorn[21] were the first to describe neoplasms in the second category, i.e. hypercalcemia associated with neoplasms without evidence of bone involvement, either by roentgenogram, bone biopsy or at necropsy. The original

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From the Section of Endocrinology and Metabolism and the Section of Oncology, Division of Medicine.

description included tumors of the kidney, lung, ovary, uterus and lymphoma. They were impressed with the frequent occurrence of hypophosphatemia, a finding which may present problems in differential diagnosis. Of the 10 patients reported three of the patients had relief of hypercalcemia with removal of the tumor and in one of these the hypercalcemia returned with recurrence of the tumor. The other 7 had inoperable tumors. Since then, the number of tumors of similar types has been expanded.[9, 22–28] as well as the addition of other types of tumors including bladder,[29,30] liver,[31] vulva,[32] and pancreas.[33] Reversibility of the hypercalcemia with removal of the neoplasm was also reported by Abouav[24] in an ovarian tumor and by Schatten[32] for a vulvar carcinoma.

PATHOGENESIS

The usual explanation for the source of hypercalcemia in neoplastic disease has been tumor cell replacement of bony tissue resulting in release of calcium,[11] which is then excreted mainly through the kidneys.[34,35] If the released calcium exceeds the capacity of the kidney to excrete the calcium, hypercalcemia ensues. Pearson[36] states that hypercalcemia does not appear until, urinary excretion of calcium exceeds 500 mg./24 hours, but occasionally[37] the amount can go as high as 900 mg. without hypercalcemia developing. In most of these latter cases osteoblastic reaction is present in bone, so that bone production may have a role in maintaining normocalcemia. Also, changes in renal reabsorptive mechanisms may be important.[12] Other authors[9,29] have emphasized the importance of rate of tumor growth in the development of hypercalcemia. Slow growing tumors may gradually cause considerable bone destruction without an elevated serum calcium, whereas with rapidly progressive osteolytic metastases the breakdown of bone with subsequent calcium load exceeds the kidneys' clearance mechanism and hypercalcemia ensues.

In the tumors without evidence of bone involvement, several theories have been postulated regarding its etiology. In all of Plimpton and Gellhorn's patients the parathyroids were normal and they speculated that the tumor elaborates a circulating parathormone-like or vitamin D-like substance. They also raised the possibility of a serum calcium-binding substance which might transport calcium in excess of the usual serum levels. However, they were unable to demonstrate such a substance.[21]

Although it is evident that hypercalcemia of malignancy is only rarely associated with anatomic abnormalities of the parathyroid gland,[11] it does occur. Parathyroid hyperplasia has been noted to occur in patients both with[4,7,38,39] and without[23,28] osseous involvement. The proposed explanation for the association of parathyroid hyperplasia and hypercalcemia in these few cases is that the tumor produces a substance X,[39] which stimulates the parathyroid gland to elaborate parathormone. Although this theory appears feasible, parathyroidectomy in one case[38] produced no response and in a second case showed only temporary response.[39] This assumption thus remains purely speculative.

DIAGNOSIS

The signs and symptoms of hypercalcemia[1,40] are non-specific and apply to all the various hypercalcemic states regardless of cause. Symptoms of hypercalcemia include weakness, dysphagia and constipation which are due to hypotonia of smooth and striated muscle. The gastrointestinal symptoms are anorexia, nausea and vomiting, which are thought to be central in origin. Symptoms referable to the renal system include polyuria and polydipsia which are very common and reflect impairment of concentrating ability because of changes in the metabolism and structure of cells lining the collecting tubules.[41] In longstanding cases there may be renal colic and hematuria from renal calculi and as a consequence, urinary tract infection may occur. Roentgenographic findings can reveal evidence of ectopic calcifications which occur in almost any location, such as arteries, stomach, or lung, but especially in the kidney. There may be renal calculi, or even more specifically nephrocalcinosis[42] which represents macroscopic aggregates of calcium in the renal pyramids and strongly suggests hypercalcemia. Symptoms related to the central nervous system vary in type and severity from mild drowsiness, lethargy and insomnia to severe occipital headaches, confusion, psychotic behavior, and even coma. Other associated symptoms include bitter taste, dryness of nose, and weight loss.

The signs of hypercalcemia include manifestations of depressed muscle function, such as hypotonicity of muscles, hyperextensible joints, depressed tendon reflexes, or transient facial palsies. Ectopic calcifications may be found in the conjunctiva or cornea (band keratopathy). Cardiovascular changes may be noted, with tachycardia and later development of cardiac arrhythmia. The electrocardiographic findings in hypercalcemia are a shortening of QT interval which is inversely proportional to the calcium level up to 16 mg.%. A prolongation of the PR interval is often observed.[43] Cardiac arrhythmias may also be demonstrated.

Because of its non-specificity, the diagnosis of hypercalcemia is often missed. The most important point is to think of the diagnosis in any patient with osseous lesions, especially if bedridden. The development of any combination of anorexia, nausea and constipation with polyuria and polydipsia, and with mental or neurologic abberations, suggests the presence of hypercalcemia.

In most cases of metastatic disease the diagnosis is obvious. However, in spite of this fact the most difficult problem in the differential diagnosis of hypercalcemia is distinguishing non-metastatic malignant tumors and tumors with obscure metastases from primary hyperparathyroidism.[9,10,20–22,24,27,31–33,44,45] At times the primary site of the tumor or evidence of metastases is not easily demonstrable and bony metastases rarely may resemble osteitis fibrosa cystica.[46] Patients with neoplasms operated upon in an unsuccessful attempt to find a parathyroid adenoma[21,27,32,33,44] attest to this mimicry.

If these two conditions are so easily confused, then what clinical features and/or laboratory studies can we use to separate these two hypercalcemic states? Both entities may be characterized by hypercalcuria, and although occasionally lower in hyperparathyroidism than in cancer (for a comparable serum calcium), it is not reliably so.[47] The serum phosphorus is classically low in hyperparathyroidism and, while the level of serum phosphate in metastatic bone disease is slightly higher than normal,[10] there are cases reported with hypophosphatemia associated with hypercalcemia of malignancy with bone metastases.[9,38,48] In any of the hypercalcemic states the development of renal insufficiency leads eventually to an elevated serum phosphorus. The percent tubular reabsorption of phosphate is reduced in hyperparathyroidism (normal 83-95%), but this test also yields low values in hypercalcemia of malignancy.[46,47,49] The intravenous calcium tolerance test was used by Thomas[49] to differentiate hyperparathyroidism from normals, but when he and others[47] attempted to differentiate the response in hyperparathyroidism from other causes of hypercalcemia, including malignancy, they were unsuccessful. Lloyd and Rose[50] proposed that an increase in the percentage of ionized calcium could be used in the early detection of hyperparathyroidism. However, determinations of ionized calcium (60% of total serum calcium in normals[1,51]) by Walzer[52] in hyperparathyroidism and hypercalcemia of malignancy revealed that in both cases the percentage of ionized calcium to total calcium remained the same despite hypercalcemia of various degrees. Thus, the percent of ionized calcium cannot be used to differentiate these two diseases. The serum alkaline phosphatase is not helpful in differentiation since it may be normal or elevated (bone and/or hepatic involvement in metastatic cancer) in either disease. However, an interesting observation was made by Griboff et al.,[15] who found that in patients with hypercalcemia secondary to bone metastases there was an inverse relationship between the serum calcium and alkaline phosphatase activity. They also found suggestive evidence that the onset of hypercalcemia was preceded by a premonitory fall in the alkaline phosphatase.

The laboratory studies mentioned thus far have not been of aid, but despite these difficulties, there are some clinical features and tests which are helpful. The rapidity of onset of symptoms of hypercalcemia may be useful. The acute onset of hypercalcemic symptoms tends to occur more frequently in malignant disease,[11,33,44] perhaps related to rapid breakdown of bone as suggested by Gutman[9] and Myers.[29] The acute onset of symptoms has also been reported in hyperparathyroidism,[53,54] but this is unusual and careful questioning reveals that all these patients had longstanding symptoms, i.e. acute superimposed on chronic manifestations. Cortisone or its analogs have been used to differentiate between hyperparathyroidism and other forms of hypercalcemia.[55,56] The hypercalcemia of malignancy, with or without metastases, may respond to corticosteriod administration with a return to normocalcemia; however, failures have also been observed.[21,33,47,49] Until recently there were no reported cases of hyperparathyroidism in which the hypercalcemia improved with corticosteroids, i.e. false positives. However, in 1961 Gwinup[57] described a single case in which a patient with a proven parathyroid adenoma was responsive to cortisone preoperatively. Of more specific aid in differentiation is the use of a bone biopsy. Even without demonstrable lesions on x-ray, one may find evidence of tumor or of bone destruction with increased osteoblastic and osteoclastic activity compatible with hyperparathyroidism. Other laboratory studies which might point specifically to hyperparathyroidism are reabsorption of bone of distal phalanges or distal portions of clavicles on roentgenogram or indentation of esophagus by a parathyroid adenoma on barium swallow. These studies, unfortunately, are only positive in 10 per cent of less of cases. Thus, one can readily see that in special cases there are considerable problems involved in differentiating these two entities and it is necessary to use all the clinical and laboratory tools available in order to make a diagnosis.

DIFFERENTIAL DIAGNOSIS

The other causes of hypercalcemia can generally be distinguished more easily. Milk alkali syndrome is characterized by a longstanding history of duodenal ulcer treated with absorbable alkali and large quantities of milk, with a normal urinary calcium, and a serum P that is generally elevated. Hypervitaminosis D is suspected when a history of ingestion of vitamin "pills" in inordinate amounts is obtained, along with a normal or elevated serum P. In hyperthyroidism signs and symptons of hypermetabolism associated with a goiter point readily to the diagnosis. Sarcoidosis is suggested by mild constitutional symptons, uveitis, generalized adenopathy, skin lesions, roenthenographic evidence of pulmonary disease and/or bone involvement, hypergammaglobulinemia, and may be confirmed by biopsy. In adrenal insufficiency, abnormal pigmentation, hypotension, and hypoglycemic attacks, along with alteration in serum sodium-potassium ratio and low 17 hydroxycorticosteroids, should present no problem in the differential diagnosis of hypercalcemic states.

MANAGEMENT

The management of hypercalcemia may represent a major problem in the care of patients with cancer. Treatment should be undertaken with an understanding of certain basic facts and then applied to the circumstances present in a specific clinical case. Several approaches to therapy of hypercalcemia of malignancy are available. Medical management plays an important role and corticosteroids are considered to be the therapy of choice. The latter has been found effective in reversing the hypercalcemia in neoplastic disease, but only in about one-half the cases.[29] Studies[36] have shown that corticosteroid treatment may produce objective evidence of tumor regression. Thus, it has been felt by some that the effect of corticosteroids in correction of hypercalcemia is due to a direct anti-tumor effect with reduction of tumor-induced osteolysis.[29] However, in tumors which are known to be unresponsive to corticosteroids this drug has been helpful in improving hypercalcemia. This may be due to a renal effect with reduction in tubular reabsorption of calcium.[58,59] Cortisone, 300-400 mg. daily, or prednisone, 60-100 mg. daily, are used. A response should occur within two weeks and longer periods of treatment usually are ineffective in reversing the hypercalcemia. Chemotherapeutic agents, which have a specific action, such as hormones, alkylating agents, antimetabolites, antibiotics, etc., if effective, can return the serum calcium to normal by direct action on the tumor, thus stopping bone breakdown. Although androgens or estrogens may induce hypercalcemia, cases[60] have been reported in which therapy has been continued with subsequent documented regression of bone disease and return to normocalcemia. Disodium ethylenediamine-tetra-acetate (EDTA), a powerful chelating agent, has been used in treatment of hypercalcemia[61] and, although effective, the results are only transient, requiring daily infusions. Also, renal tubular damage has been reported associated with its use.[62] Certain general measures including activity, in order to reduce any additional bone breakdown with immobility, adequate hydration, to balance the losses of fluid due to polyuria, plus a low calcium intake (200 mg. of calcium daily) are of great importance and not to be overlooked in the therapy of hypercalcemia of malignancy.

The treatment of associated problems should also be discussed. The synergism between calcium and digitalis, with respect to the myocardium is well known, and care should be exercised in digitalization of a patient with hypercalcemia. The cautious use of digitalis and following the patient with serial electrocardiograms will help to minimize the hazards. Renal insufficiency may occur in the course of hypercalcemia and thus one must apply the same medical principles of treatment as one would in therapy of renal failure due to any other cause.

Surgery for the non-metastatic tumors with hypercalcemia (Gellhorn type), if operable, should correct the calcium elevation.[21,22,24,32] In estrogen-dependent breast cancers, ablative procedures have been shown to be of definite value in the correction of hypercalcemia.[36,63] In fact, Schwartz[1] refers to a patient who actually developed hypocalcemia following adrenalectomy for breast cancer with osseous metastases, while previously demonstrating hypercalcemia. This presumably was because of marked avidity of the bones for calcium in the rebuilding process ("hungry bones"). Myers[29] feels it is best to control the hypercalcemia with other forms of therapy before ablative surgery, but that moderate elevations in serum calcium do not contraindicate surgery. Another approach in this type of patient would be radiation castration, although probably less reliable than surgery. It is of interest to note that Albright reported a case[48] of a patient with a solitary osseous lesion where radiation therapy was effective in correcting the chemical abnormality. This, however, would appear impractical in cases with diffuse osteolytic lesions.

Most physicians have a passive attitude towards the complications of malignancy, including hypercalcemia. Yet it has been shown many times that when hypercalcemia is treated adequately, that a prolonged and useful survival has occurred. Even more rewarding are the long term regressions that occur in some of these patients, as a result of subsequent specific chemotherapy.

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Internal mammary route. The internal mammary veins normally empty into

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OBSTRUCTION OF THE SUPERIOR VENA CAVA

E. Wilson Staub, M.S.,M.D.

Although superior vena caval obstruction may produce a classic syndrome, it occurs uncommonly enough and in such varying patterns to occasionally escape diagnosis. Congestive heart failure, angioneurotic edema, allergic blepharitis, lymphedema, obesity, and nephritis are a few of the misdiagnoses which may mislead the unaware clinician. It is the purpose of this review to refresh the reader with the historic, anatomic, etiologic, diagnostic and therapeutic aspects of this challenging clinical entity.

HISTORICAL REVIEW

In 1757, William Hunter described and illustrated the postmortem findings in a man who died on October 29, 1752: ". . . *x*, the vena cava superior, and *y*, the common trunk of the left subclavian and jugular vein (were) both so much compressed by the dilated artery as hardly to have anything left of their natural capacity and appearance."[1] Thus, what is probably the first described case of superior vena caval obstruction was caused by aneurysm. McIntire and Sykes[2] were able to find in the writings of Thomas Bartholinus in 1740[3], reference to the case of a man who died from suffocation and in whom a "small bit of flesh with shapeless fat in the orifice of the vena cava" was found. They felt, however, the reference was vague and there was no statement as to whether the material was in the inferior or superior vena cava.

As outlined by Fischer[4], and Ehrlich, Ballon and Graham[5], Corvisart (1806) reported marked narrowing of the superior vena cava, and Marjolin (1819) reported complete obliteration of that vessel. Deckert (1823), Weissbrod (1831) and Poschel (1903) further contributed to the literature on the subject. In 1902[6] and 1903[7], William Osler described three cases of superior vena caval obstruction caused by aneurysm, Hodgkin's Disease and fibrous obliteration, and included a diagram of the collateral circulation thought to be present in the last case.[7] In 1904, Fischer[4] summarized 252 cases which had been reported to that time. McIntire and Sykes,[2] in 1949, published an excellent review of the literature from 1904 through January, 1946 listing 250 cases and adding two of their own. Numerous additional articles on the subject have appeared since then.

ANATOMY OF THE SUPERIOR VENA CAVA[8, 9]

The superior vena cava forms by the convergence of the two innominate veins at the inferior border of the first costal cartilage, and terminates in the right atrium at the level of the third right costal cartilage in front and the seventh thoracic vertebra behind. It measures

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From the Division of Surgery.

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seven to eight centimeters in length in the adult. Somewhat less than half of the vessel is contained within the pericardium, which reflects obliquely over it just below the entrance of the azygous vein posteriorly. Its only other tributaries are small veins from the mediastinum and pericardium.

The superior vena cava is in close relationship to many major intrathoracic and mediastinal structures. In front, it is covered by the thymic remnant and is overlapped by the right pleura and lung. Behind, are the azygous vein, the right pulmonary artery, and the superior right pulmonary vein. To the right side, are the right lung and pleura, and the phrenic nerve; and, to the left side, the ascending aorta and innominate artery. Several groups of lymph nodes are in intimate proximity, including the right superior set of anterior mediastinal nodes (which lie near the phrenic nerve), and the peritracheal and right peribronchial nodes. The superior vena cava is effectively encased by the lymphatic system which drains the structures of the entire right and lower left thoracic cavities.[10–12]

COLLATERAL CIRCULATION

The collateral circulation of the superior vena cava is abundant. There are four major systems involved, each of which intercommunicates with the others.[2,8,13–15]

Azygous route. The azygous vein, which normally empties into the superior vena cava, receives blood from: a), the right ascending lumbar vein; b), the right intercostal veins, except for the superior two or three which enter the superior intercostal vein, which then empties into the azygous vein; c), the hemiazygous vein, which, with the accessory hemiazygous vein and the left superior intercostal vein, communicates with the left intercostal veins; and, d), small esophageal and posterior mediastinal veins. The left superior intercostal vein also frequently communicates with the left innominate vein. The lumbar veins communicate with the common iliac veins and the inferior vena cava.

Internal mammary route. The internal mammary veins normally empty into their respective innominate veins. In superior vena caval obstruction, however, the flow is reversed, and blood is carried to the lower part of the body through the many communications of the internal mammary veins. These communications include: a), the inter-costal veins, which communicate with the azygous system and inter-vertebral veins; b), the superior epigastric veins, which communicate with the inferior epigastric veins; c), musculophrenic veins; and, d), by perforating branches to the superficial veins of the thorax.

Vertebral route. This system consists of a complex, interconnecting group of internal and external vertebral venous plexuses. There are communications with: a), the dural sinuses; b), vertebral veins (which empty into the innominate veins); c), intercostal veins; and, d), lumber veins.

Lateral thoracic route. The superficial veins of the upper thorax form a diffuse plexus, the major named vessel being the lateral thoracic vein, which empties into the axillary vein. This plexus communicates with the subclavian veins above; and, below, to the thoraco-epigastric, superficial epigastric, and superficial circumflex iliac veins. Perforating branches communicate with the internal mammary veins in front, the intercostal veins laterally, and the posterior external vertebral venous plexus behind.

LOCATION OF OBSTRUCTION

Obstruction of the superior vena cava may occur in one of three anatomical ways: 1), above the azygous orifice; 2), including the azygous orifice; and, 3), below the azygous orifice. The collateral circulation varies with each location.[2,13,14] When the obstruction is above the orifice of the azygous vein, this vessel becomes enlarged and is the principle venous trunk through which blood returns to the heart from the upper part of the body. The intercostal veins receive blood from the mammary veins, upper vertebral plexuses, and, by perforators, from the superficial thoracic plexus. The communications with the inferior vena cava through the lumbar and superficial abdominal veins are not particularly well developed.

When the obstruction includes the azygous orifice, this vessel does not enlarge, and the flow of blood is reversed. The other three routes are the most important, and superficial veins become strikingly distended.

An obstruction below the azygous orifice results in a shunting of blood through all routes, but conspicuously so through a massively enlarged azygous vein, in which the direction of flow is reversed. Figure 1. is the chest x-ray of such a patient. The high right hilar shadow is a dilated azygous vein. At thoracotomy a tense fibrous band was constricting the superior vena cava at the pericardial reflection.[16]

The effects of acute occulsion of the superior vena cava have been determined in dogs. Occlusion above the azygous orifice is well tolerated, and an extensive collateral circulation develops.[13] Occlusion below the azygous orifice is poorly tolerated, all animals dying within four hours with venous pressures up to 65 mm Hg, arterial hypotension, elevated spinal fluid pressure, cerebral edema, and flattening of the EEG patterns.[13,17,18] One case of acute vena caval obstruction following cardiac surgery terminated fatally with cerebral edema and brain infarction.[19] In dogs, occlusion below the azygous orifice is tolerated for periods up to two hours.[17,18] Clamping of the superior vena cava was tolerated in one patient for forty minutes during resection and graft replacement.[20]

ETIOLOGY

The major causes of obstruction of the superior vena cava are neoplasm, aneurysm, medistinal inflamation, and thrombosis. For the present review, 445 cases were summarized from reports appearing since 1946, but is admittedly not exhaustive. This tabulation is compared with Fischer's series of 1904,[4] and McIntire and Sykes' series of 1904 to 1946 (Table I).

Neoplasm. Neoplasms are currently responsible for three-fourths of all superior vena caval obstructions, a significant increase from the previous series. All but a very few are malignant, and almost 85% of these are carcinomas of the lungs and bronchi. Table II summarizes the types of neoplasms in the three series.

Benign intrathoracic tumors causing superior vena caval obstruction are distinctly unusual. The list includes "benign" teratomas,[21,33,38] intrathoracic goiters,[28,37] and a chemodectoma.[43]

Of pulmonary tumors causing superior vena caval obstruction, about 80% arise in the right lung, with the right upper lobe and right mainstem bronchus predominating.[23,29,37,64] Szur[29] found superior vena caval obstructions in 14.6% of 732 patients with carcinoma of the bronchus. Roswit, Kaplan, and Jacobson[23] reported an incidence of 15% in patients treated with irradiation, and Schecter,[25] 11% of 210 cases of proven bronchogenic carcinoma. Steinberg and

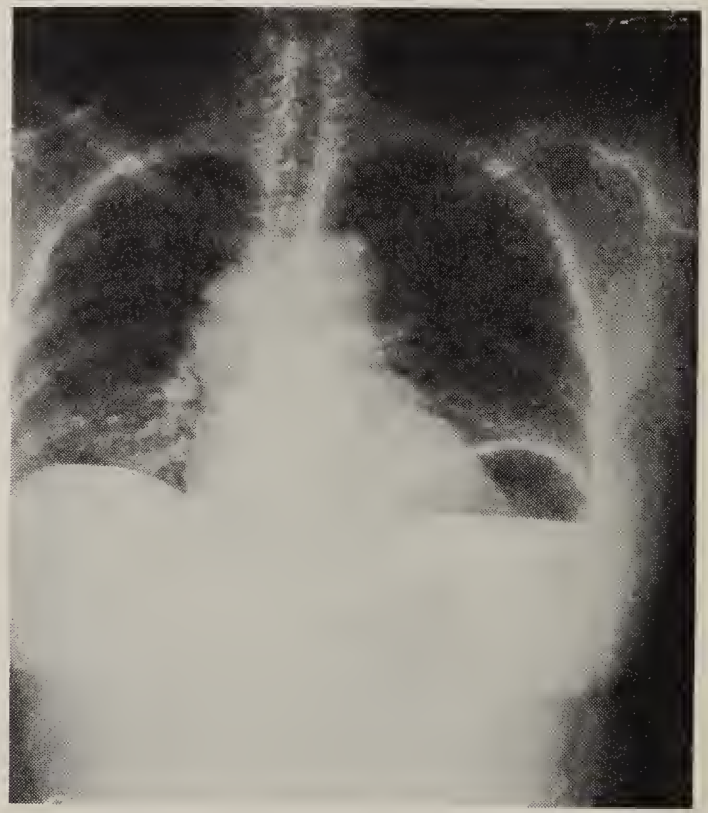

Fig. 1.—The abnormal shadow in the upper part of the right hilum proved to be a dilated azygous vein. At thorocotomy a resectable, constricting band was present at the pericardial reflection below the azygous vein, in which the blood flow was reversed. (Courtesy of Drs. E. J. Beattie, Jr., N. Tillney and E. Dainko.)[16]

TABLE 1

ETIOLOGY OF SUPERIOR VENA CAVAL OBSTRUCTION

ETIOLOGY	Fischer[4] TO 1904 (252 cases)	McIntire and Sykes[2] 1904-1946 (250 cases)	Present Series (445 cases)	References to Present Series
NEOPLASM	50.0%	37.6%	75.0%	21–43
ANEURYSM	36.0%	24.0%	6.1%	21–23,25,28,44,45
MEDIASTINITIS	6.0%	24.8%	11.2%	21,25,31–33,36,37, 39,40,46–60
THROMBOSIS	5.5%	9.2%	1.6%	21,31,32,61
OTHERS, OR NOT STATED	2.5%	4.4%	6.1%*	16,21,22,37,62
TOTAL	100.0%	100.0%	100.0%	

*Includes two cases of pericardial band[16,21]

TABLE 2

TYPES OF NEOPLASM CAUSING SUPERIOR VENA CAVAL OBSTRUCTION

NEOPLASM	Fischer (76 cases)	McIntire and Sykes (76 cases)	Present Series (260 cases)	References to Present Series
BENIGN	7.9%	4.0%	3.1%	21,28,33,37,38,43
MALIGNANT Pulmonary	73.8% (all)	29.0%	84.6%	21,23–33,37,39,41
Lymphoma		38.2%	5.0%	21,23,25,32,33
Thymoma		6.6%	1.9%	21,25,32–34
Sarcoma		9.2%	1.2%	23,33
Other intrathoracic neoplasms		6.5%	0.4%	33
METASTATIC	18.3%	6.5%	3.8%	21,23,31–33,37,56
TOTAL	100.0%	100.0%	100.0%	

Dotter[65] found involvement of the superior vena cava in varying degrees in 17% of one hundred patients studied angiographically preoperatively. The pulmonary tumors causing superior vena caval obstruction are generally of the anaplastic variety with unusual growth potential.[23,37,64] Postmortem examination of vena cavas obstructed by these tumors reveals the wall to be directly invaded in almost all cases, rather than merely compressed by contiguous tumor or occluded by thrombus.[23,25,33,64,65] Rosenbloom[64] found that seven of eight patients with bronchogenic carcinoma died three to ten weeks following onset of superior vena caval obstruction. The outlook is indeed bleak in this group.

Other malignant tumors represent only a mere handful by comparison. It is notable that lymphoma is being reported less frequently as a cause of superior vena caval obstruction, perhaps because of earlier diagnosis and effective treatment, and because of the increase of pulmonary cancers.

Surprisingly, metastatic tumors only infrequently obstruct the superior vena cava. This group includes testicular teratoma,[5] hepatoma,[32] neuroblastoma,[21] fibrosarcoma of the thigh,[56] and thyroid,[23] pancreatic,[23] cervical,[33] mammary,[23,37] and adrenal[3] carcinomas.

Aneurysm. Although many textbooks still list aneurysm of the aorta and innominate artery as a frequent cause of superior vena caval obstruction, the incidence has dropped considerably since the onset of effective anti-syphilitic therapy. They occur almost exclusively in males, and are almost always syphilitic.

Mediastinitis. Mediastinitis was responsible for 11.2% of superior vena caval obstructions in the current series, which marks a decline from McIntire and Sykes' report of 24.8%. Fischer's figure of 6.0% may have been due to the paucity of diagnostic methods for syphilis and tuberculosis before the turn of the century, and "chronic fibrosing mediastinitis" was not described until after his review.[2]

Syphilis,[32,47,58] tuberculosis,[25,32,33,54,49] and histoplasmosis[37,62] have been indicted in some cases for the chronic mediastinal inflammation which, in the subacute stage, consists of dense granulomatous lesions, and gradually becomes matted, fibrosed and collagenous. Occasionally only a few constricting bands of fibrous tissue remain. Often, however, the responsible agent is not identified or suggested by smears, histologic sections, culture, skin or serological testing.[37,63,67] A history of recurring respiratory infection is often obtainable in many of these obscure cases.[2,68,69] There are also reports of mediastinal fibrosis with superior vena caval obstruction following irradiation to the mediastinum.[31,53]

Thrombosis. Thrombosis of the superior vena cava is a rather unusual occurrence as an isolated event, albeit contributory in the other three groups. Thrombosis has been described following trauma,[21,31,53] carbunculosis of the chest,[70] and in association with cardiac disease, silicosis, and tuberculous endophlebitis.[2]

SEX AND AGE INCIDENCE

Obstruction of the superior vena cava is a male problem in a ratio of about four to one. Fischer[4] found that 71.3% were males, McIntire and Sykes[2] reported 79.5% males, and in the present series of cases for which the sex was listed, 87.4% were males. Some of the male predominance in the present group may be due to the increasing incidence of bronchogenic carcinomas as the etiologic agent, and several series which were written from Veterans Administration Hospitals. Slightly over 70% of cases were in the 30 to 60 year age group, the fifth decade being the most common. Fischer found three cases below the age of ten years, McIntire and Sykes only one, and there were four cases in the present series.[47,55,61,62]

SYMPTOMS AND SIGNS[2,5,21–23,32,37]

Increased venous pressure in the areas of the body drained by the superior vena cava produce the clinical picture associated with superior vena caval obstruction. The severity of symptoms and conspicuity of signs depend on the completeness and abruptness of the occlusion, and extent of development of collateral circulation.

The patient may complain of puffiness of the face and eyelids, which is most marked on arising in the morning and improves during the period of erect posture. Shirt collars become tight. There may be tinnitus, dizziness, fainting, and a fullness in the head, aggravated by stooping or bending over. Epistaxis may occur. Dyspnea is often present in more severe cases, the best explanation for which is venous stasis and resultant accumulation of metabolites in the respiratory center.[72] Unusual presentations of patients have included bleeding esophageal varices,[59] hydrocephalus in an infant,[62] and Jacksonian epilepsy.[71]

If the obstruction comes on suddenly,

spinal fluid pressure rises rapidly. Cerebral edema results in faulty cerebration and even coma.[5] Glottic and laryngeal edema may be terminal events.

The soft tissues of the head, neck and upper extremities are swollen (Figure 2.). The eyes tend to bulge, and conjunctival edema may be present. Venous engorgement results in a ruddy cyanosis which is exaggerated by coughing, straining, lying down, or bending over. The peripheral venous system responds to the obstruction by dilatation of the superficial veins of the trunk. This is especially well demonstrated by infrared photography (Figure 3.). Telangiectasis over the anterior chest and upper abdomen is common. Extensive tumor may cause Horner's syndrome, vocal cord paralysis, phrenic nerve paralysis, and widening of the mediastinal dullness. Estimation of venous pressures in the upper and lower parts of the body is the most important feature toward reaching a sound preliminary diagnosis.

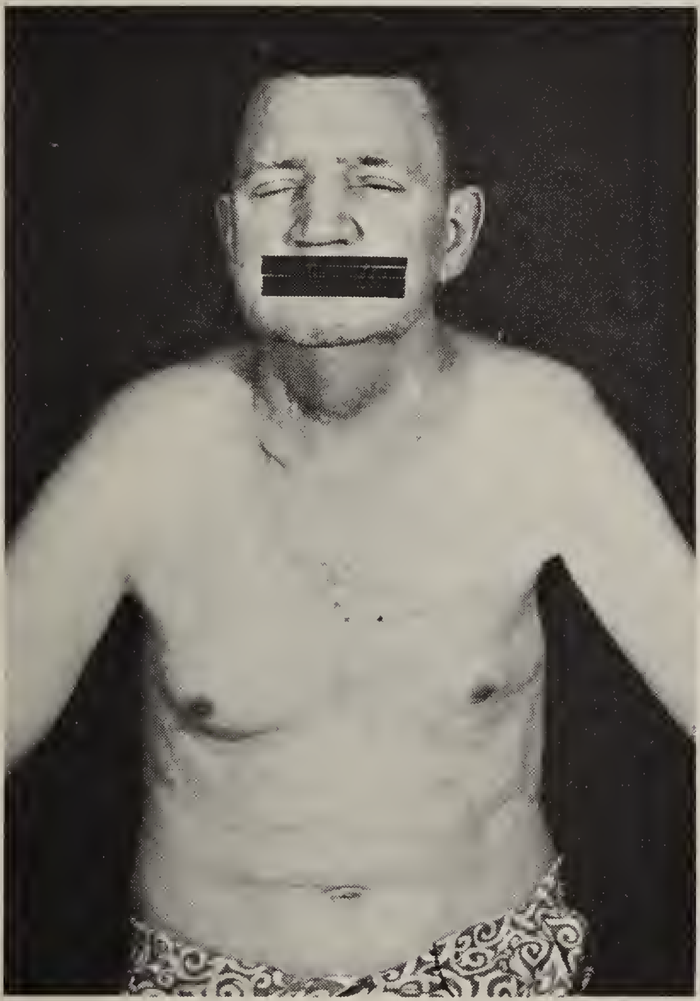

Fig. 2—This middle-aged male was admitted with plethora and swelling of the upper trunk, arms and face. This was most marked on arising, gradually improving during the day. (Courtesy of Dr. E. J. Beattie, Jr.)

DIAGNOSIS

Superior vena caval obstruction is suspected on history and physical findings, and is confirmed by direct measurement of venous pressures in the upper and lower parts of the body. Normal venous pressure in the antecubital vein ranges from 50 to 150 mm. of normal saline.[22] It rises slightly during expiration (increased intrathoracic pressure), and falls during inspiration (decreased intrathoracic pressure). Venous pressure in the femoral veins, on the other hand, *rises* slightly during inspiration and falls during expiration (decreased intra-abdominal pressure during passive expiration). The finding of a rise during inspiration in the upper extremity venous pressure suggests that blood is being drained to the inferior vena cava.[73]

Another supplemental observation of venous pressure is the exercise test.[74,75] The hand is forcefully opened and closed for one minute, while measuring venous pressure in that arm. The increase in blood flow is normally well-accommodated by venous dilatation, venous pressure remaining stable, even in the presence of heart failure. If there is proximal venous obstruction, however, venous dilatation is already at a maximum, and venous pressure rises, usually more than ten mm. of saline. Moreover, the rate of rise during exercise, and the rate of fall on cessation of exercise, yield an indication of the completeness of the occlusion and the state of development of the collateral circulation. Decholin circulation time is prolonged.[28]

When the etiology of the obstruction is a mediastinal mass, conventional chest roentgenograms will demonstrate a widening of the mediastinum, particularly in the anterior-superior compartment. A pulmonary neoplasm may be seen as a separate lesion, often in the right upper lobe, or as a contiguous mass in the hilum (Figure 4.). Hilar and mediastinal calcific shadows are suggestive of a chronic inflammatory process. Laminography may be helpful in delineation of the mediastinal structures.

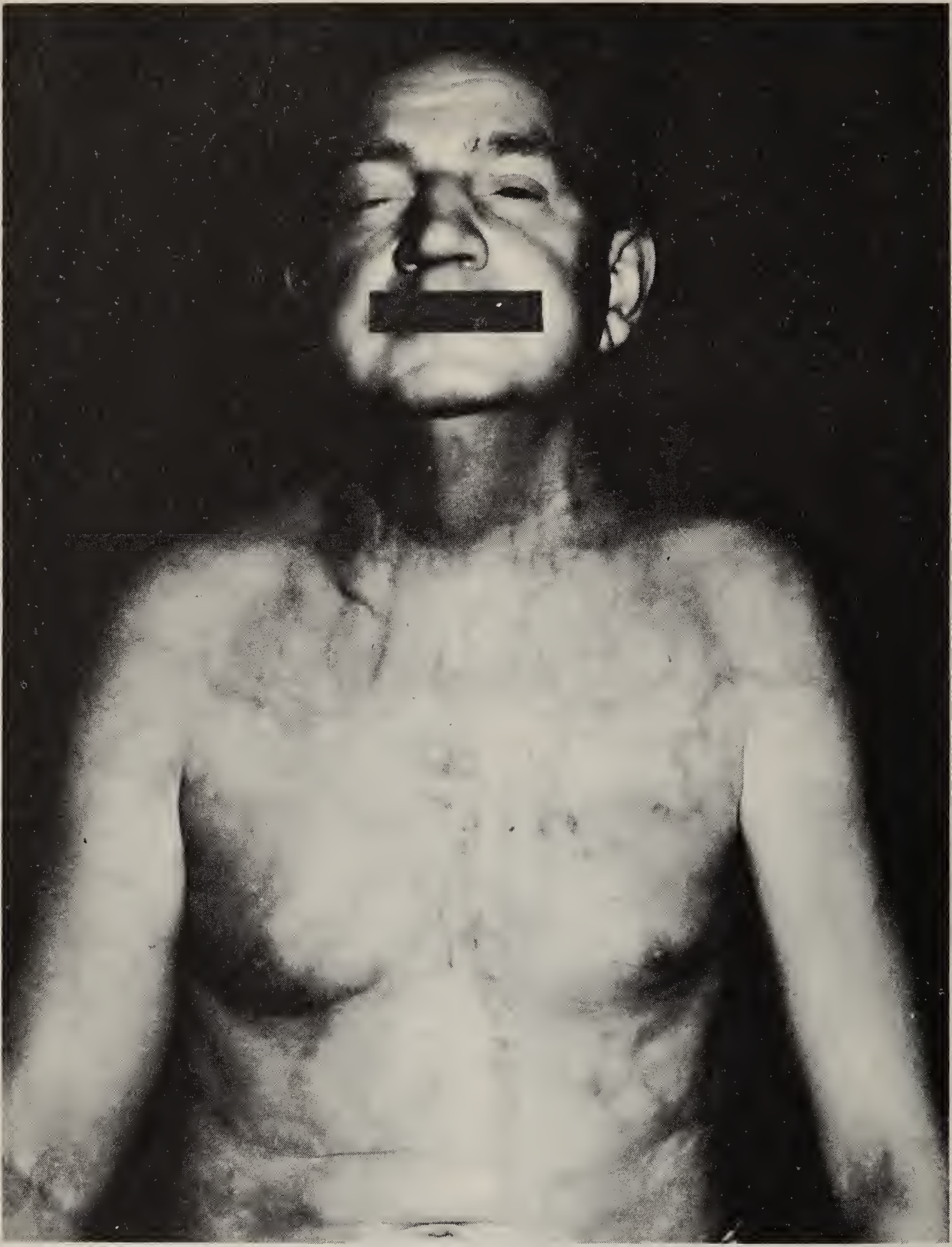
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Fig. 3.—Infrared photography accentuates the superficial venous pattern seen in superior vena cava obstruction. (Same patient as Figure 2.)

The techniques and value of phlebography to demonstrate the site of obstruction and the nature and extent of the collateral circulation have been described by several authors.[76–81] The technique consists essentially of the injection of radiopaque material into a proximal vein, usually one or both antecubital veins, with appropriately timed exposures, preferably in rapid succession. Figure 5. is the result of an injection in a distended anterior jugular vein, and demonstrates a displaced, compressed, and probably invaded superior vena cava, as well as extensive collateral formation over the anterior chest. When aneurysm of the aorta or innominate artery is suspicioned, confirmation by aortography is indicated.

Additional information may be obtained by the study of sputum cytology, which should be positive in a bronchogenic carcinoma advanced enough to result in superior vena caval obstruction. Bronchoscopy may be undertaken in cases where glottic and laryngeal edema are not present. Lymph node biopsy can become a major undertaking (as can tracheostomy) in the presence of marked venous hypertension, but may be very helpful when enlarged nodes are clearly palpable. Skin tests and sputum culture are only occasionally helpful.

TREATMENT

The indication for therapy depends on the severity of symptoms and prognosis, which in turn depend upon the site and

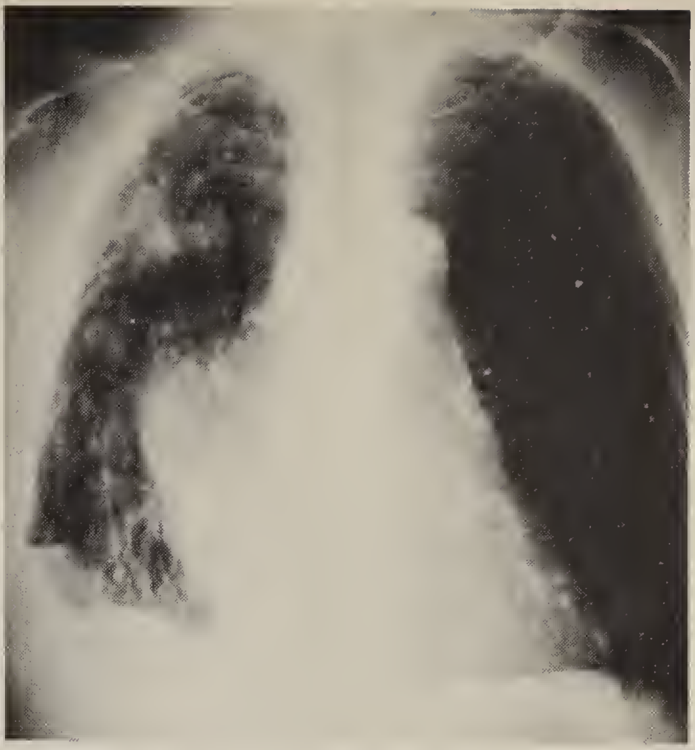

Fig. 4.—This chest roentgenogram of a patient with superior vena caval obstruction demonstrates a large mass in the right hilum. This proved to be a highly malignant bronchogenic carcinoma.

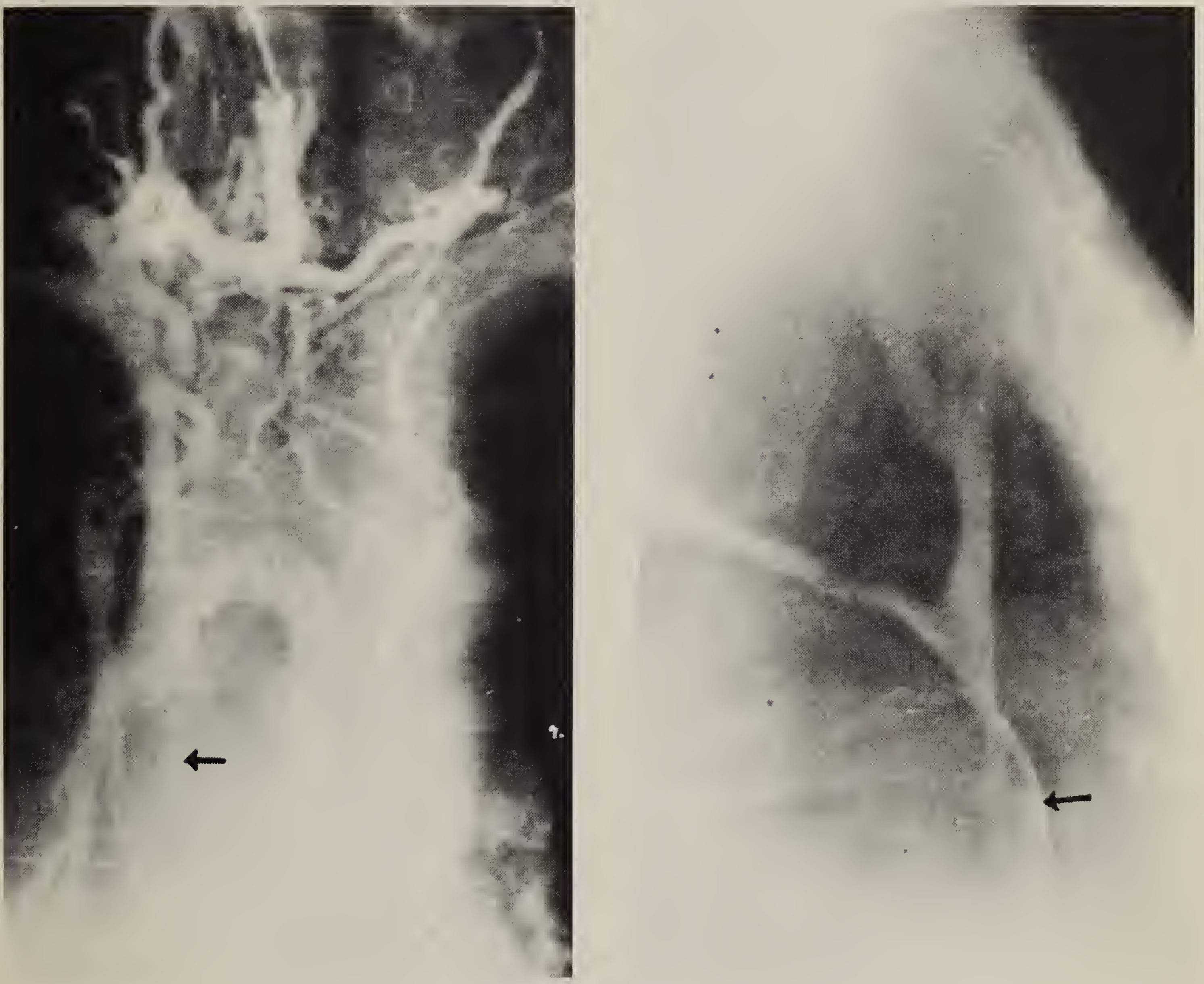

Fig. 5.—Phlebography is useful to demonstrate the site and extent of superior vena caval obstruction. The superior vena cava is compressed anteriorly and probably invaded by tumor below the entrance of the azygous vein (arrows). Extensive collateral circulation is also evident.

completeness of the obstruction, the rapidity of onset, the ability of the patient's collateral circulation to assume the task of transporting the obstructed blood, and the responsible etiology. Obstruction of the superior vena cava is not necessarily incompatable with long life, providing, of course, the etiology is not malignant. McCord, Edlin and Block[48] described a patient who was alive 50 years following onset of the obstruction. Glushien and Mansuy[82] reported a patient after 36 years, Bruckner[32] after 28 years, and Murdock and Will[58] after 19 years.

Symptomatology may be improved by the administration of diuretics, elevation of the head of the bed, and, in severe cases, by phlebotomy.[2] A significant number of cases will improve spontaneously as adequate collateral develops and should recannulation of a thrombosed vessel occur. Nevertheless, a significant proportion of patients remain moderately to severely symptomatic and are grateful indeed if their obstruction is relieved. Specific therapeutic measures include irradiation and chemotherapy (for malignant obstructions), and various surgical procedures.

RADIOTHERAPY AND CHEMOTHERAPY

These measures are obviously designed for patients with malignant obstruction of the superior vena cava. Roswit, Kaplan and Jacobson[23] reported a satisfactory remission of symptoms in 76% of 36 patients. They employed tumor doses averaging 3,600 r in most of their patients, using nitrogen mustard (.3 to .4 mg/Kg) when irradiation was unfeasible or ineffective. The average remission was ten weeks, and the longest was one year. Effler and Groves[37] reported the survival for one year of eight patients, with two still alive after four years, following cobalt-60 teletherapy. (The tumor types were not stated, however.) On the other hand, Calkins[28] found that irradiation added little or nothing to comfort or survival. Favorable results for irradiation in lymphoma[32] and malignant thymoma[21] are reported, possibly because the mode of obstruction is usually compression rather than direct invasion.

Interestingly, Schecter and Ziskind[66] described the postmortem pathological findings in patients who had clinically benefited from irradiation and/or chemotherapy, discovering that the vena caval walls were infiltrated with tumor and obstruction was complete in all cases. They suggested that "a good clinical response in vena caval obstruction due to carcinoma and other infiltrative diseases depends on the efficiency of the collateral circulation, chiefly the azygous vein." Willis[83] reported a single lymphoma case in which the superior vena cava was infiltrated by tumor.

SURGICAL PROCEDURES

Certain selected cases of superior vena caval obstruction are amenable to surgical attack, for which a number of procedures have been devised. The simplest situation is when the obstruction is caused by a fibrous band, sometimes at the pericardial reflection, division of which affords relief[16,21,68]. Mediastinal decompression, resection of granulomas, tumors or fibrous masses, endvenectomy, and replacement or by-pass of the superior vena cava are other occasionally effective procedures.

Mediastinal decompression

The first record of a surgical procedure for superior vena caval obstruction would seem to be that of Guleke's, who, in 1929, reported the relief of symptoms following median sternotomy in a case of an obstructing aortic aneurysm.[84] In 1934, Ehrlich, Ballon and Graham[5] described the case of a comatose 24 year old female with superior vena caval obstruction caused by Hodgkin's disease. The right fourth and fifth costal cartilages were excised in their entirety and a small amount of tumor removed. In less than three hours following surgery the patient regained consciousness, and within 24 hours the patient's head and arm edema had disappeared. Higginson[56] reported transient relief in a case of metastatic fibrosarcoma. Conversely, Tubbs[85] commented unfavorably on this procedure.

Excision of granulomas, fibrous masses and tumors

In 1936, Ochsner and Dixon[86] reported a case of superior vena caval obstruction caused by post-traumatic fibrosis. Constricting scar tissue was resected, with a drop in venous pressure and marked clinical improvement. Others have subsequently reported success with resection of fibrotic mediastinal tissue[2,55,60,68], while other attempts have been unsuccessful[46,87]. Effler and Groves[37] have stated that they do not advise surgical treatment in cases of chronic mediastinitis with superior vena caval obstruction, but suggest "prophylactic" resection of granulomatous mediastinal nodes and tissue during the subacute phase—before dense scarring has taken place. They claim that in no instance has the pleural cavity been contaminated by spilled nodal content, nor has superior vena caval obstruction subsequently occurred.

Klassen, Andrews and Curtis[21] reported the successful resection of an obstructing mediastinal teratoma. Complete relief of symptoms resulted. An obstructing syphilitic aortic aneurysm has been successfully resected and grafted, again with relief.[45]

Endvenectomy

Four cases have been reported in which occluding material within the lumen of an obstructed vena cava has been surgically removed. In 1954, O'Neill[89] reported his surgical procedure on a female patient who had had symptoms of superior vena caval obstruction for almost ten years. At operation a woody mediastinitis was found. The superior vena cava was opened and the "well-organized scar of thrombus-like material was rongeured from the inside of the vein." This procedure resulted in relief of symptoms. A similar procedure was performed by DuBost[90] with success. Templeton[39] reported two cases of endvenectomy of the superior vena cava. In one, dense fibrotic material was excised from within the vessel with return of a venous pressure of over 300 mm saline to normal and successful follow-up three years later. In the second case, malignant tumor was removed from within the vein. Relief was obtained for one year before recurrence.

Replacement and by-pass by graft

a. Clinical experience. An increasing number of cases in which the superior vena cava has been replaced or by-passed have appeared in the literature since Klassen, et al.[21] reported a case in which the patient's own superficial femoral vein was used to establish a shunt between the azygous vein and right atrium. The graft was patent by phlebography six months later. A series of reported clinical cases in which a graft was employed to replace or by-pass an obstructed or resected superior vena cava is summarized in Table III. Although the list has a higher precentage of successes than failures, it is not unreasonable to assume that a higher percentage of the former are more likely to be reported. Schramel and Olinde's case[91] represented an interesting operation in which the saphenous vein was mobilized in the leg and the distal end anastomosed to a dilated external jugular vein. The patient experienced relief of the vena caval obstruction until succumbing to his malignancy.

b. Experimental replacement of the superior vena cava. Perhaps a more accurate appraisal of caval grafting and choice of material might be possible from a review of experimental studies. Table IV summarizes the results with various replacement materials. Most of the work has been performed in dogs. The best materials appear to be autogenous vein, autogenous thoracic aorta (obviously impractical in man), Teflon, and rigid-weave Dacron. Figure 6. is the venacavagram of a dog in which the superior vena cava was replaced with autogenous left iliac vein six months previously.[94] Several factors appear to increase the likelihood of success: meticulous anastomotic technique, synthetic tubes should be of large diameter and of rigid material or externally supported, ligation of the azygous vein in dogs to increase the flow through the graft, and end-to-end anastomoses. It is also of interest that autogenous vein grafts may recanalize after initial thrombosus.[40] Of supplemental interest, Riberi, Pompey and Hritzo[108] successfully patch-grafted the superior vena cava in twelve dogs with fine mesh nylon.

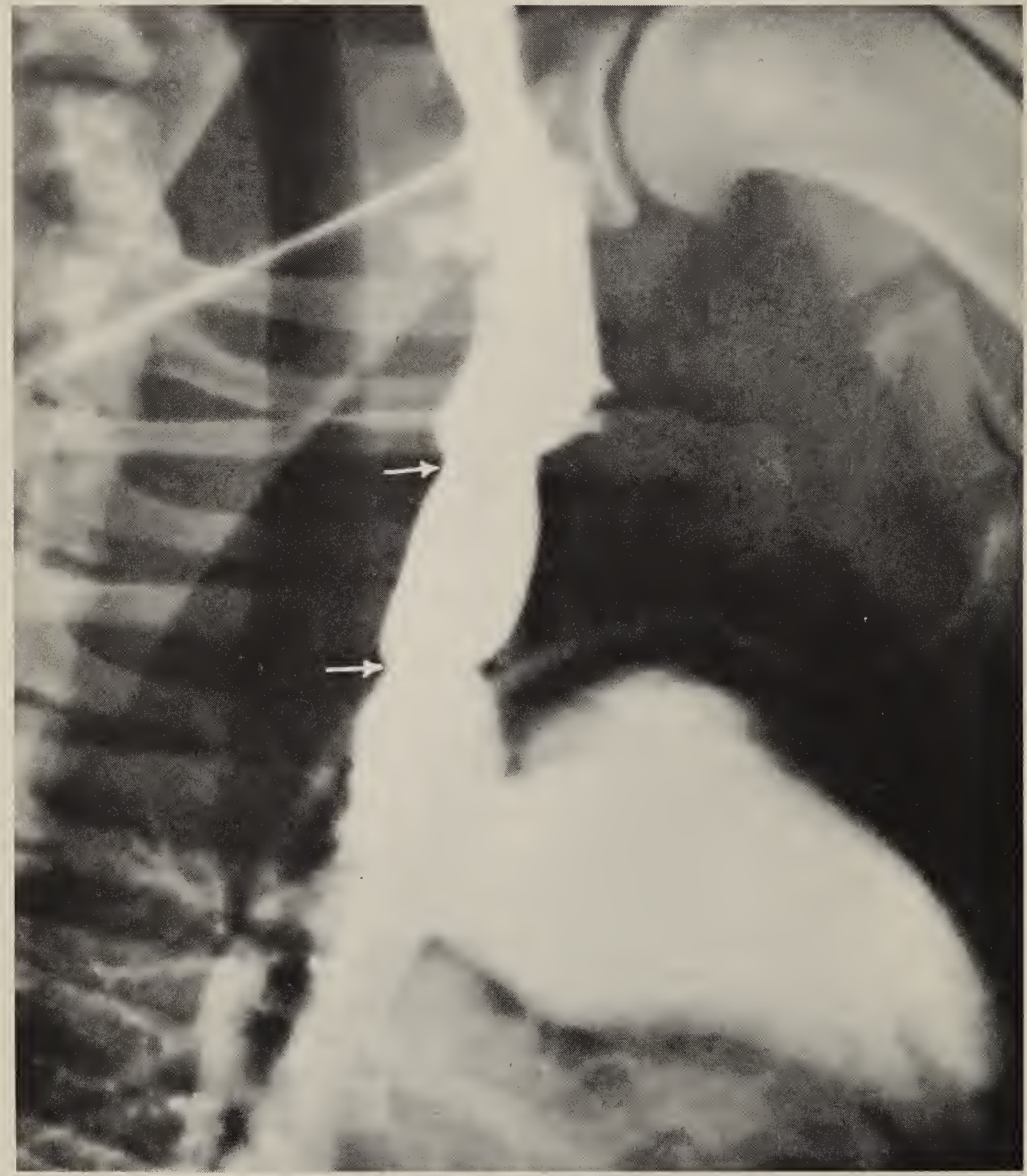

Fig. 6.—Autogenous iliac vein was used to replace a segment of superior vena cava in this dog six months prior to venacavagram. There is some narrowing at the anastomoses, but jugular venous pressure is normal, and there is no evidence of collateral circulation.

TABLE 3

SUPERIOR VENA CAVAL REPLACEMENT OR BY-PASS: SUMMARY OF CLINICAL CASES

TYPE OF GRAFT	FOR TUMOR		FOR MEDIASTINAL FIBROSIS	
	SUCCESS	FAILURE	SUCCESS	FAILURE
AUTOGENOUS VEIN	1 yr.[42] 6 wk.[91]	5 yr.[51] 5 mo.[52]	6 mo.[21], 1 yr.[53] 8 da.[53], 1 yr.[31] 2 yr.[36]	5 yr.[51] 5 mo.[52] PO death[31] ?[31], ?[88]
HOMOLOGOUS AORTA	4 mo.[24], 3 mo.[26] 4 mo.[56]*, 6 wk.[56] 5 mo.[31]		5 yr.[49,54] 10 mo.[50] 11 mo.[56] 5 mo.[31], 5 mo.[31]	1 mo.[31] 4 yr.[40]
PORCINE AORTA	7 mo.[27]			
TEFLON	2 yr.[36], 7 mo.[20] 7 mo.[62], 1 yr.[43]	15 mo.[40]	4 mo.[36]	
IVALON			Pt. improved-patent?[57]	
CRIMPED NYLON			4 mo.[31]	

*[56]: showed marked sclerotic changes.
Data show length of follow-up and reference

TABLE 4

EXPERIMENTAL REPLACEMENT OF THE SUPERIOR VENA CAVA

TYPE OF GRAFT	No. patent/No. experiments (REFERENCE)	COMMENT
AUTOGENOUS VEIN	0/4[54]*, 0/3[92], 2/2[93] 0/?[49], 0/7[40]** 9/17[40]***, 15/17[94]***	*Panelled graft **Azygous patent ***Azygous ligated
AUTOGENOUS THORACIC AORTA	33/33[95]	High post-operative mortality—impractical in man
AUTOGENOUS PERICARDIAL TUBE	0/4[92], 0/12[96]	
HOMOLOGOUS AORTA	0/25[97], 4/4[54], 5/5[27] 6/13[98], 32/37[99], 4/6[93]	Grafts frequently stenotic and wrinkled; degeneration seen microscopically
HOMOLOGOUS VEIN	0/6[97], 0/3[51], 25/35[101]*	*Some follow-ups quite brief
BOVINE AORTA TO CANININE SVC	9/11[61]	Follow-up 2 days to 1 year
TEFLON	16/19[103]*, 6/7[104] 12/16[105]**, 57/78[106]***	*11 others died early **4 others died early ***90% of ⅝" and ¾" grafts were patent
NYLON	2/10[99], 6/7[104]*	*All were partially obstructed
IVALON	0/4[54], 0/6[92]	
TREATED DACRON	24/32[107]	9/14 with less rigid weave 15/18 with rigid weave

SUMMARY AND CONCLUSIONS

Obstruction of the superior vena cava is interesting, variable, and challenging. The first case was recorded by William Hunter in 1757. Since then about a thousand cases have appeared in the literature.

The anatomy of the superior vena cava is such that it is vulnerable to disease processes involving the ascending aorta, innominate artery, several groups of lymph nodes, thymus, tracheobronchial tree and the right lung. Collateral circulation of the superior vena cava occurs via four principal routes: the azygous, the internal mammary, the vertebral, and the lateral thoracic (superficial) routes. Each of these intercommunicates with the others.

Obstruction of the superior vena cava may occur at one of three sites: above the azygous vein orifice, including the azygous orifice, or below the azygous orifice. The development of collaterals through the various routes will vary with the site and completeness of the obstruction. Obstruction at or below the azygous orifice will result in reversal of blood flow in the azygous vein.

There are four main causes of superior vena caval obstruction: neoplasm, aneurysm, mediastinitis, and thrombosis. Neoplasms currently account for approximately three-fourths of the cases, 90% of which are due to carcinoma of the lung. The site of origin of the pulmonary tumors is most frequently in the right lung, particularly the right main stem bronchus and right upper lobe. They tend to be of a highly malignant, anaplastic type.

Symptoms and signs of superior vena caval obstruction result from venous hypertension in the upper trunk, head and arms, consisting essentially of venous distention, cyanosis, edema and pain. Severity of the symptoms will depend upon the abruptness of onset, extent and completeness of the obstruction, and state of collateral circulation. Common complaints include increase of shirt collar size, dizziness, fainting, fullness in the head, tinnitus, and puffiness of the face and eyes. Many of the symptoms are aggravated by stooping or bending over.

Diagnosis is made by direct pressure measurements. The venous pressure in the upper half of the body is higher than below, and may have the fluctuation characteristics of the inferior vena cava during respiration. The site of obstruction and extent of collateral circulation may be determined by phlebography. Work-up to determine the etiology of the obstruction may variably include the following: chest roentgenograms, mediastinal laminograms, angiocardiography or aortography, bronchoscopy, sputum cytology, skin tests, and, in selected cases, thorocotomy. It has been suggested that if the syndrome has been present for more than six months, the etiologic agent is benign.[52]

Treatment is variable. Many cases will improve spontaneously as collaterals develop. Symptomatic measures include diuretics, elevation of the head of the bed, and, in severe cases, phlebotomy. Radiotherapy and chemotherapy have been advised for most malignant obstructions, although there is evidence to suggest that once the superior vena cava is invaded by tumor radiotherapy will not reopen it. Selected cases may respond favorably to surgical measures, which have included division of constricting bands, resection of compressing masses, mediastinal decompression, endvenectomy, and vena caval replacement or by-pass.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

A Correlation of Clinical and Hemodynamic Studies in Patients with Mild and Severe Anemia with and Without Congestive Failure, J. S. Graettinger, R. L. Parsons, and J. A. Campbell, *Annals of Internal Medicine 58: 617-626, April, 1963.*

Clinical and hemodynamic studies in 25 patients with moderate and severe anemia at rest and during exercise have been presented. In addition to the usual findings in the patients with severe anemia, the data obtained also demonstrate definite hemodynamic abnormalities during exercise in the patients with moderate anemia. Clinical "congestive failure" was present in 2 patients but was not accompanied by the usual hemodynamic evidences of myocardial inadequacy. The relationship of circulatory loads, including anemia, to cardiac performance and congestive failure is discussed. Restoration of normal blood cells during the hemodynamic study of a third patient without evident heart disease resulted in the occurrence of both clinical and hemodynamic evidence of myocardial inadequacy.

The Immune Mechanism of Transplantation and possible Role of DNA and RNA. T. Y. Sabet and R. D. Ray, *"Bone Biodynamics" Henry Ford Hospital Symposium, March, 1963.*

Some of the basic immunological concepts concerning transplantation of bone have been reviewed.

The possible role of RNA in the transfer of immunity has been investigated by the use of RNAase. The results revealed that the treatment of hyperimmune spleen or lymph node cells with RNAase did not interfere with their capacity to transfer hypersensitivity to bone and skin grafts.

The need for additional studies on a cytochemical level has been stressed.

Multilocular Cysts of the Kidney in Children. E. A. Dainko, W. R. Dammers, and S. G. Economou, *The Journal of Pediatrics, Vol. 63, No. 2, pp. 249-255, Aug., 1963.*

A case of a unilateral multilocular cyst of the kidney in a 22-moth-old child is presented. Multilocular cysts of the kidney are rare, this case being the tenth in the pediatric age group reported in the literature. Multilocular cysts of the kidney are differentiated from multicystic disease, polycystic disease, and simple cyst of the kidney. A set of criteria for categorizing multilocular cysts is reiterated. Some proposed theories of etiology of renal cysts are mentioned. Multilocular cysts of the kidney most commonly present as abdominal masses found on a routine examination and are most often misdiagnosed as Wilms's tumors. Hematuria is seen less frequently. The treatment is nephrectomy or simple resection where the opposite kidney is absent or insufficient.

Catastrophic Loss of the Scalp and Contiguous Structures. J. W. Curtin, Lt. Comdr. W. D. Latham, mc, usn, P. W. Greeley, R. E. McNally, *Jour. of Plastic and Reconstructive Surgery, Vol. 32, No. 1, July, 1963.*

There appears to be a need to reappraise the long term results of skin graft coverage of the scalp following catastrophic losses. The surgical literature has many examples of the successful initial care of the enormous scalp wound subsequent to traumatic or surgically acquired avulsions. What is not mentioned is the failure of the split-thickness skin graft to "wear well" as a scalp covering over a long period of time. The extended story is one of minor traumatic incidents followed by ulceration, cellulitis, osteomyelitis and progressive breakdown that can only be cured by replacement with a more adequate and substantial skin and subcutaneous covering. Based on their experiences with such cases the authors feel serious consideration should be given to elective exchange of the potential unstable split-thickness skin graft with large pedicle flaps. Where the loss of scalp has been extensive, pedicle flaps by necessity must come from more distant parts of the body. Three representative cases demonstrate the use of the large marsupial pedicle flap in varied conditions.

Enzyme Studies on Sulfhydryl Inhibitors for Cancer Therapy. F. E. Knock, *Surg. Gyn. Obst., 117,172, Aug., 1963.*

In both agar plate assays and time lapse cinemicrography studies. the sulfhydryl inhibitor mapharsen alone or with adjuncts has been more toxic than conventional drugs to living human cancer cells from solid tumors and to blood cells of leukemic patients. Because of this in vitro activity of mapharsen against a variety of human tumors and the suggestions of clinical benefit from chemotherapy with mapharsen plus chemical adjuncts in a small series of terminal cancer patients, mapharsen has now been selected as a standard against which newer sulfhydryl inhibitors specifically designed and synthesized for this program will be judged. Effects of large amounts of mapharsen on normal tissues in dogs are presented. Infusion of varying doses of mapharsen plus adjuncts above celiac artery in dogs and direct intrahepatic injection of the drugs in dogs produce measurable rise in serum enzymes, especially sorbitol dehydrogenase and isocitric dehydrogenase. Care must be used in interpreting clinical data since rapid regression of large amounts of some human tumors by chemotherapy with mapharsen plus adjuncts can also be associated with high serum levels of the enzymes.

The cornerstone of this coordinated surgical-chemical program for treatment of disseminated cancer remains assay of chemical effects against living cancer cells from each patient. Because huge masses of cancer doom chemotherapy for most solid tumors, tumors are now being first reduced maximally by resection, electrocautery or cryogenic congelation before chemotherapy is given by direct intratumor injection at surgery followed by intraarterial infusion or intravenous chemotherapy after surgery with the combination of drugs and adjuncts shown best by in vitro assay against the patient's own tumor. At present, each cancer patient appears to be an individual problem in chemical kinetics for whom total surgical-chemical therapy must be individualized in accord with chemical reactions of his own cancer cells.

Migration of Aortic Prosthesis into the Duodenum. *Case report and Review,* L. Long, J. A. Hunter, and W. S. Dye, *Annals of Surgery, Vol. 157, No. 4, April, 1963.*

A case report is presented detailing the course of events which resulted in unique complications following abdominal aortic bifurcation reconstruction for arteriosclerotic obliterative disease, with a Dacron Graft. Ultimately this graft which had become infected, eroded into the duodenum and became entirely intraluminal in the intestine. Death was due to hemorrhage resulting from digestion of the pseudo-intima of the prosthesis and leakage of blood through the interstices of the porous graft into the duodenum. During the course of events the digested and disrupted psuedo-intima of the graft dissected and acted as an embolus to the right femoral artery.

The case histories and reasons for rupture of 48 abdominal aortic grafts that have ruptured into the gastrointestinal tract are reviewed from literature. Conclusions are reached regarding the technical aspects of prevention of this disastrous complication, the diagnosis of this rare complication when it has occurred and finally the method of treatment when aortico-enteric fistula exists.

La Reparacion Cirugica Plastica De Lesiones Benignas Y Malignas De La Piel. P. W. Greeley, *Proceedings Segundo Congreso, Mexicano De Dermatologia, April, 1963.*

This presentation discusses the plastic surgical treatment and repair of benign and malignant lesions of the skin.

Consequences of Creation of Arteriovenous Fistula. Orthopedic and Cardiovascular Effects in a Patient with a Shortened Leg. A. D. Meyer, J. J. Muenster, J. H. Olwin, F. S. Shapiro, and J. S. Graettinger, *Journal of the American Medical Association 184: 611-615, May 25, 1963.*

Serial orthopedic and hemodynamic measurements made in a child before, during and after the creation of a systemic arteriovenous fistula to promote growth of a shortened leg are reported. The surgical approach was that developed by Janes and his co-workers at the Mayo Clinic. The mechanisms and associated clinical phenomena of the hemodynamic load imposed by the fistula are discussed. This procedure may be to date the most effective method for diminishing the disparity between the two limbs. In a child with a normal heart the creation of such a fistula may impose no cardiac hazard; however, in some children, especially those with cardiac disease, there may be serious cardiovascular consequences. This procedure requires at all stages the close collaboration of the orthopedic surgeon, the vascular surgeon and the cardiologist.

Parliament Hoodwinked by Joanna Stephens. E. L. Strohl, *Surgery, Gynecology & Obstetrics, Vol. 116, 509-511, April, 1963.*

The blatant exploitation of the British public in the 18th century, by Joanna Stephens, a vulgar, unlettered, yet shrewd woman, stands at the pinnacle of quackery of the world.

The most troublesome ailment of that era was stone in the bladder and kidneys, and Joanna's claim that she had discovered a remedy for the ailment was given credence by some of the most distinguished persons of the time, the press, and eminent writers.

Her supporters importuned British Parliament to grant the 5,000 pounds demanded by Mrs. Stephens for her secret remedy, and the commission appointed by Parliament, which attested to the efficacy of her prescription, was composed of outstanding individuals, among whom were three prominent surgeons, Cheselden, Hawkins and Sharp. Parliament voted 5,000 pounds for what was found to be a combination of egg shells, snails, herbs, soap, swines' cresses, wild carrot and burdick seeds, ashen keys, honey, hips and hawes.

Postmortem examinations on 12 patients of Joanna disclosed stones in the bladder. The postmortem examination on Sir Robert Walpole, a devotee of Joanna Stephens, was carried out by Caesar Hawkins. He found three large stones in Sir Robert's bladder, and it was calculated that an otherwise intelligent Prime Minister had consumed nearly two hundredweight of soap and the equivalent of 1,200 gallons of limewater.

A review of the sums spent by the public for present day potions, elixirs, pills, and other equally valueless nostrums, does not compliment our enlightened and scientific twentieth century or the cultural level of the people.

Induction of Resistance to Sarcoma 180 Tumor in Mice. T. J. McNair, E. Hoppe and W. H. Cole, *Archives of Surgery, Vol. 86, pp.196-198, Feb., 1963.*

We have compared the effect of incubation of 440,000 Sarcoma 180 cells for 24 hours in guinea pig serum, and a similar number of cells incubated in rabbit serum on growth of the cells. Each mixture was inoculated every other day for 3 injections, subcutaneously into Swiss mice. "Takes" were sustained in 20% of 30 mice receiving the 3 injections of cells and rabbit serum, compared to 100% of 30 mice injected with cells and guinea pig serum. When these animals receiving the 3 injections of attenuated cells were challenged with fresh Sarcoma 180 cells, the "takes" were much lower than in the control animals receiving fresh cells only, but complicating factors (e.g., "take" or "no take" following injection of attenuated cells) makes interpretations difficult.

Type-Specific Antibody Response in Man to Injections of Cell Walls and M Protein from Group A, Type 14 Streptococci. C. K. Wolfe, Jr., J. A. Hayashi, G. Walsh, and S. Barkulis, *Jour. of Lab. and Clin. Medicine, Vol. 61, p. 459, March, 1963.*

Severe local and systemic reactions have characterized human immunization attempts with products of Group A Streptococcus. In dealing with this problem, the authors have administered both cell wall suspensions and acid-extracted M protein (in mineral oil adjuvant) to demonstrate the production of type-specific antibodies to Type 14, Group A streptococci in humans. Skin testing with small doses of saline-suspended cell walls showed that 15 patients (out of 107) were unduly sensitive, and they were excluded from the study. Of the remainder, 38 individuals received up to 43.2 mg. of streptococcal cell walls suspended in saline; 9 individuals received up to 4.8 mg. of cell walls precipitated from alum solution; and 12 persons received up to 2.4 mg. of cell walls in mineral oil emulsion. In addition, 19 patients received a preparation of M protein in mineral oil. In this last group, there was a good yield of primary antibody responses (63%) to relatively small amounts of M protein (900 mg. or less), whereas the other schedules of administration evoked a secondary antibody response. This study contrasts the various materials and dosage schedules which evoke a type-specific response in human serums to the Group A. Streptococcus, paralleling the successes of a similar project in rabbits. The method of choice is considered to be the use of acid-extracted M protein in combination with mineral oil adjuvants. Skin reactivity was not related to the immune response; and patient tolerance of emulsion form of vaccine was considered to be fair.

Correct Time, Sequence and Technic for Closure of Cleft Lip and Palate. L. W. Schultz, *Jour. Int. Coll. of Surg., Vol., 39 No. 6, June, 1963.*

The author emphasizes the importance of early closure of cleft lip and palate—an otherwise normal child 2 weeks old, in his opinion, is not too young—not only on the basis of improved functional and cosmetic results, but because of the elimination of repeated operations. He also deplores the current custom of having children with these abnormalities treated at the same time by a number of different specialists, which, in his opinion, causes great confusion and apprehension in parents and may easily lead to serious complications, delays, technical errors and flawed final results.

Superior Mesenteric Artery Syndrome. J. S. Hyde, C. L. Swarts, E. E. Nicholas, C. R. Snead and N. F. Strasser, *The Amer. Jour. of Diseases of Children, Vol. 106, pp. 25-34, July 1963.*

The small number of patients and the brief follow-up time does not allow us to make definitive claims about the efficacy of medical therapy of SMAS. The effectiveness of surgery is, however, a strong argument in favor of early operative intervention.

Pediatric patients with recurrent episodes of postprandial abdominal pain should be suspected of having SMAS. Once the diagnosis of SMAS is suspected it may be confirmed by fluoroscopy.

In our series, surgical therapy consisting of mobilization and downward displacement of the distal duodenum appears to be the most successful treatment.

The Surgical Significance of Trauma to the Pancreas. E. L. Strohl, R. J. Baker, W. F. Dippel, and R. J. Freeark, *The Archives of Surgery, Vol. 86, pp. 1038-1044, June, 1963.*

The pancreas is one of the last unconquered organs within the abdomen. This soft, fragile, strategically located retroperitoneal structure, having internal and external secretion, remains a technical enigma, notwithstanding the profound advances that have been made in other areas of abdominal surgery.

Despite the difficulties in management, when the pancreas is injured by blunt or penetrating trauma, definitive treatment often must be carried out. In an effort to resolve the dilemma surrounding appropriate surgical measures, 79 surgically proven cases of traumatic pancreatic injury, encountered at the Cook County Hospital, were reviewed. Of these, 57 patients were treated for penetrating injury and 22 for blunt trauma.

The signs and symptoms suggestive of pancreatic injury in blunt trauma were detailed. The criteria which have been established for surgical exploration in suspected lesions are enumerated.

The location of the injury, the traumatizing agent, and the associated wounds of adjacent organs were assessed as to the incidence of complications, and their role in the current mortality rate. The operative management of pancreatic wounds was analyzed, and the available procedures discussed.

The sequelae of pancreatic damage, whether preventable or non-preventable, and the principles of care in injury to various segments of the gland are documented.

The surgical principles of significance which were emphasized are: (1) exploration of the abdomen is essential when significant amylase elevation occurs after blunt trauma; (2) adequate exposure of the pancreas can only be accomplished by opening the gastrocolic omentum; (3) aggressive management of pancreatic injury, especially if ductal disruption and hemorrhage are present, is advocated; (4) adequate drainage of the lesser omental bursa with suction of the sump type must always be instituted.

In Vivo and in Vitro Assay for Drug Effect on Cancer Cells. G. O. McDonald, A. N. Stroud, A. M. Brues and W. H. Cole, *Annals of Surgery, Vol, 157, No. 5, May, 1963.*

The effect of anti-cancer drugs upon DNA and RNA synthesis in the Ehrlich ascites tumor was investigated. Changes in the rate and extent of incorporation of tritiated thymidine and tritiated uridine was followed during the 48 hours following drug treatment. There was close correlation between the depression of DNA synthesis and the in vivo effect of each drug upon growth of the tumor. Depression of RNA synthesis also was observed and appeared to be correlated with drug effect but was not as sensitive or as constant as was the effect upon DNA synthesis. The clinical application of this prodecure was described.

Diverticulitis of the Colon. M. M. Romsdahl and W. H Cole, *Archives of Surgery, Vol. 86, pp. 751-760, May, 1963.*

The surgical management of diverticulitis of the colon has been reviewed from the standpoint of symptomatology, clinical findings, surgical indications, and results of therapy. Pain was the most frequently presenting symptom, and obstruction represented the most common indication for operation. Roentgenographic stenosis of the sigmoid was commonly found without antecedent history of perforation, as were abscess formation and fistulae. While the apparent trend is toward earlier operation and single-stage procedures, surgical management of patients by stage procedures, with colostomy, is safer when acute inflammation of the bowel or other serious complications are present.

Reserpine: Its Effect on Silver-Stained Structures of the Heart. E. F. Hirsch, *Science, Washington D.C., Aug. 9, 1963.*

The administration of reserpine to dogs in doses sufficient to deplete myocardial catecholamines resulted in alterations in the affinity of the heart for silver stain. Most noticeably affected was the "perimysial plexus."

The Juvenile Amputee. C. N. Lambert, *The Illinois Medical Journal, Vol. 123, No. 5, pp. 514-517.* May, 1963.

This article deals with the definition of a Juvenile Amputee being one who is not yet skeletally mature and points out the difference between the juvenile and adult amputee. The chief factor in this difference is the further growth potential in the child.

The Juvenile Amputees are divided into two main groups, the acquired whose etiology is chiefly trauma and tumors. The larger group are those so-called amputees which the author points out are chiefly limb bud deficiencies. The age of fitting of the juvenile amputee is stressed. In acquired amputees, fitting should be done as soon after the amputation as the stump has healed. In amputations necessitated for malignant tumors, prostheses should be supplied within three months provided there are no evidences of metastases or local recurrence at that time.

In the congential group fitting of upper extremity deficiencies may be done as early as three months and in the lower extremity at about age one year when the child would normally be attempting to stand.

These recommendations are based primarily on the present case load which is as follows:

Total number of Juvenile Amputees	*509*
Congenital amputations	*278*
Acquired amputations	*231*

Subtotal Myomectomies as an Adjunct in the Plastic Surgical Repair of Facial Paralysis. P. W. Greeley, *Bol. y trab. Soc. Argent. Circujanos 24, 1963.*

This presentation is a discussion of our experience in subtotal resection of muscles of facial expression on the unparalyzed side following preliminary fascia lata support of the paralyzed side of the face in 7th cranial nerve injuries. The purpose is to slow up the activity of the normal side of the face so that a better balance of the two sides can be obtained.

PRESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN